nature reviews gastroenterology & hepatology

https://doi.org/10.1038/s41575-025-01159-4

Review article

Check for updates

Acute-on-chronic liver failure: pathophysiological mechanisms and clinical management

S. K. Sarin[1] ✉, Ashok Choudhury[1], Anupam Kumar[2], Nadim Mahmud[3], G. H. Lee[4], Qin Ning[5], Soek-Siam Tan[6], Kessarin Thanapirom[7], Vinod Arora[1], Nobuaki Nakayama[8], Jun Li[9] & Constantine J. Karvellas[10]

Abstract

Acute-on-chronic liver failure (ACLF) is a complex syndrome characterized by acute hepatic decompensation superimposed on pre-existing chronic liver disease or cirrhosis that is associated with acute worsening of portal hypertension, increased risk of infection, organ dysfunction and high short-term mortality. This Review provides a comprehensive update on definitions, pathophysiological mechanisms, clinical presentation and management of ACLF. The severe hepatic injury in ACLF triggers systemic inflammation, which is driven by damage-associated molecular patterns, gut-derived microbial products, and immunometabolic and functional dysregulation. Immune dysfunction can range from hyperinflammation and hypercytokinaemia to immune paresis, which in turn predisposes patients to infection and organ failure. The principles of ACLF management prioritize ameliorating the acute hepatic insult, managing portal hypertension, preventing organ failure and optimizing patients who are eligible for liver transplantation. Emerging options include novel therapies targeting immune modulation and liver regeneration, therapeutic plasma exchange and artificial liver support systems. Well-defined criteria for prompt interventions and selection of patients for transplantation within the first week after diagnosis — the 'golden window' — have improved outcomes of liver transplantation in patients with ACLF. The Kyoto ACLF Consensus reflects global efforts on unifying definitions, simplifying treatment end points, refining prediction tools, and filling the void of targeted non-transplantation interventions to improve outcomes in patients with ACLF; however, large knowledge gaps remain and further research is needed.

Sections

Introduction

Definitions of ACLF

The changing spectrum of ACLF aetiologies

Mechanisms of liver injury and cellular pathology in ACLF

Clinical course of ACLF

Management of ACLF

Liver transplantation in ACLF

Experimental therapies

Conclusions

A full list of affiliations appears at the end of the paper. ✉e-mail: shivsarin@gmail.com

SHOUT
SHARE
IT

Key points

- Acute-on-chronic liver failure (ACLF) is a syndrome of acute deterioration of liver function in a patient with chronic liver disease or cirrhosis with hepatic and/or extrahepatic organ failure (EHOF).
- ACLF can be broadly classified into type A (hepatic failure) and type B (EHOF).
- The nature and degree of acute insult and underlying hepatic functional reserve determine the outcome in a patient with ACLF.
- During the first week of illness (the 'golden window'), severity scores such as those defined by the ACLF Research Consortium and the European Association for the Study of the Liver Chronic Liver Failure consortium can be used to guide therapeutic decisions.
- Careful attempts should be made to preserve the function and reverse the failure of organs; protocol-based 'critical care hepatology', a multidisciplinary approach, and use of 'bridge therapies' help nearly half of patients with ACLF to survive with a native liver.
- Liver transplantation is considered the definitive therapy for ACLF, and the only life-saving treatment in very sick patients.

Introduction

Acute-on-chronic liver failure (ACLF) is a syndrome in which a rapid deterioration in hepatic function occurs in a patient with underlying chronic liver disease (CLD) or cirrhosis of the liver, and is associated with high short-term mortality[1]. Patients with ACLF have varied presentations owing to differences in underlying hepatic functional reserve (HFR), stage of CLD or cirrhosis, degree of portal hypertension, nature and severity of the acute insult, functional reserve of organs, and the status of the bone marrow, immune system, nutrition and gut microbiome[2]. HFR refers to the liver's capacity to maintain essential metabolic, synthetic, immune and regenerative functions[3]. It can be assessed by clinical features of liver failure, tests of synthetic function (such as serum albumin, prothrombin time and coagulation factors), quantitative liver function tests[4] and albumin synthesis rates using heavy water (D_2O)[5]. However, these tests cannot quantify HFR in a patient with jaundice, ascites or liver failure, limiting accurate assessment of organ injuries and precision-guided therapies for ACLF. This Review provides an update on advances in the pathogenesis, assessment and management of patients with ACLF and discusses research priorities that could progress the field.

Definitions of ACLF

Multiple definitions of ACLF exist, the most well-recognized ones being from the Asian Pacific Association for the Study of the Liver (APASL) ACLF Research Consortium (AARC) and the European Association for the Study of the Liver (EASL) Chronic Liver Failure (CLIF) consortium. The APASL definition was developed in 2009 and states that ACLF is an acute hepatic insult manifesting as jaundice and coagulopathy complicated within 4 weeks by ascites and/or hepatic encephalopathy in a patient with previously diagnosed or undiagnosed CLD or cirrhosis, and is associated with high short-term mortality[1] (Fig. 1). A core feature of ACLF in a patient with cirrhosis is the worsening of the pre-existing portal hypertension. The APASL definition provides a homogeneous phenotype of patients with a hepatic insult as an acute event and liver failure with or without other organ failure and excludes patients with previously decompensated cirrhosis, as they have a different natural history. The APASL definition does not exclude patients who fulfil the definition but also have extrahepatic organ failure (EHOF), but it does not mandate the presence of EHOF to define ACLF, which is a major distinction from other definitions.

The EASL–CLIF consortium conducted a prospective study in 1,343 patients, and proposed that ACLF is a severe form of acute decompensation in cirrhosis caused by hepatic or non-hepatic precipitants, associated with a 28-day mortality rate of 20% or more and characterized by systemic inflammation and failure of one or more of the six major organ systems: kidney, brain, circulation, respiration, coagulation and liver[6]. The EASL–CLIF grading system was based on the number of organs with failure (grade 1 being failure of one organ, grade 2 being failure of two organs, and grade 3 being failure of three or more organs), whereas APASL defined ACLF grades using the AARC score (with scores of 5–7 being AARC grade I, scores of 8–10 being grade II, and scores of >10 being grade III). Patients with decompensated cirrhosis who deteriorate rapidly are included in the EASL–CLIF definition. Although the EASL–CLIF definition does not require jaundice for ACLF diagnosis, mean serum bilirubin levels at inclusion in the CANONIC study (from which the EASL–CLIF definition came) were 7.7 mg/dl, 15.2 mg/dl and 23.2 mg/dl in patients with ACLF grade 1, grade 2 and grade 3, respectively[7], which indicates that liver failure was present in the original EASL–CLIF patient cohort.

The APASL and EASL–CLIF definitions are not the only definitions of ACLF; other definitions include those from the American Association for the Study of the Liver Diseases (AASLD), the North American Consortia for the Study of End Stage Liver Disease (NACSELD) and the Chinese Group on the Study of Severe Hepatitis B (COSSH), among others[8,9]. The definitions differ on criteria for the diagnosis of CLD and inclusion of patients with CLD, inclusion of patients who have had prior decompensation (acute or non-acute decompensation), whether patients present with liver failure and the level of jaundice, whether infection and sepsis are acute precipitating events or occur as part of the natural course of cirrhosis, and whether the presence of EHOF is essential for diagnosis (Supplementary Table 1). A lack of clarity and agreement on these issues has hindered the development of new therapies and resulted in a lack of clarity on end points for clinical trials in ACLF[10].

The PREDICT study by the EASL–CLIF consortium showed that bacterial infections and/or severe alcoholic hepatitis are the major factors in acute decompensation and ACLF in patients with acutely decompensated cirrhosis, and added the concept of pre-ACLF and stable or unstable acute decompensation (Supplementary Table 2). However, this did not help the real-world scenario, as admission criteria were not uniform ('any decompensation'), and the 90 days waiting for development of organ failure in patients with pre-ACLF is quite long given that the 28-day mortality is reported to be high[11]. The situation in a patient with cirrhosis with an index presentation of acute deterioration along with organ failure is different from the situation where a patient with decompensated cirrhosis who already has impaired organ function experiences an acute clinical worsening that leads to organ failure or a further decompensation of a decompensated cirrhosis[11]. In medicine, a disease 'entity' should be accepted only if it is distinct, the treatments for it are specific, and the outcomes in those with and without the disease entity are clearly different. Unfortunately, marked

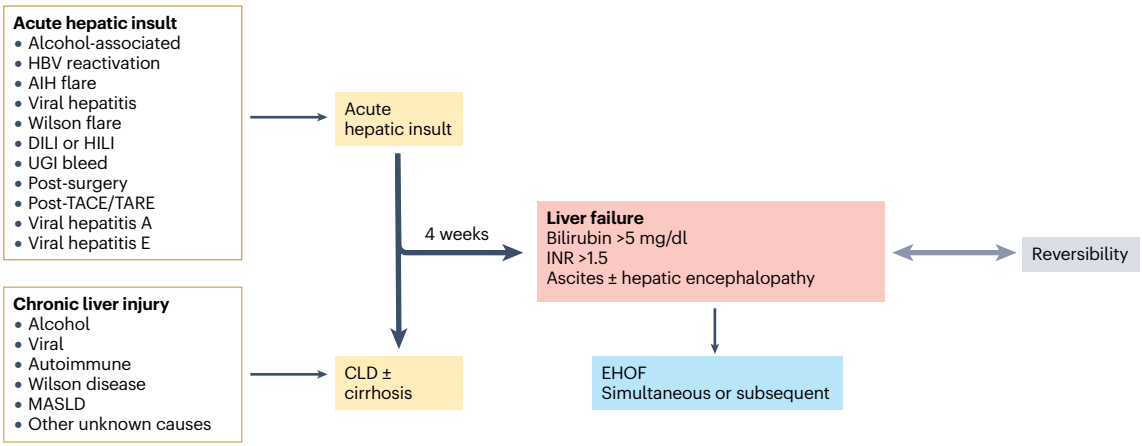


Fig. 1 | Concept of acute-on-chronic liver failure according to the Asian Pacific Association for the Study of the Liver ACLF Research Consortium. The Asian Pacific Association for the Study of the Liver defines acute-on-chronic liver failure (ACLF) as an acute hepatic insult on a background of chronic liver disease (CLD) or cirrhosis that leads to liver failure (jaundice (bilirubin >5mg/dl) and coagulopathy (international normalized ratio (INR) ≥1.5)) with or without ascites and/or hepatic encephalopathy, within a time period of 4 weeks. Liver failure can be associated with extrahepatic organ failure (EHOF), either simultaneously or subsequently depending on the severity of liver failure; EHOF is often secondary to hepatic failure rather than independent of it. Reversibility of ACLF syndrome (bilirubin <5 mg/dl, prothrombin time (PT)-INR <1.5 at 3 months), recompensation and regression of fibrosis can occur and can lead to survival with native liver. AIH, autoimmune hepatitis; DILI, drug-induced liver injury; HBV, hepatitis B virus; HILI, herb-induced liver injury; MASLD, metabolic dysfunction-associated steatotic liver disease; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; UGI, upper gastrointestinal.

overlap exists between current definitions from EASL–CLIF of acute decompensation, further decompensation, and ACLF.

An initiative by the APASL resulted in the development of the Kyoto ACLF Consensus[12], which aimed to develop a global consensus by including experts from Asia and the West. The Kyoto Consensus defines ACLF as a distinct reversible syndrome characterized by rapid-onset liver failure (bilirubin >5 mg/dl and international normalized ratio (INR) ≥1.5) followed by ascites and/or encephalopathy within 28 days associated with or without kidney dysfunction (serum creatinine >1.5 mg/dl) in a patient with CLD or cirrhosis, and is associated with high mortality within 28 days. According to this consensus, ACLF exists in two types, type A and type B (Fig. 2). Patients with type A ACLF present primarily with hepatic failure, with no mandatory EHOF, which aligns with the APASL and Japanese, Mexican and COSSH definitions. Patients with type B present with one or more EHOF, which corresponds to the EASL–CLIF and NACSELD definitions. The AASLD definition includes a type A ACLF cohort, but EHOF is mandatory in this definition.

The Kyoto ACLF Consensus also introduces a system to grade the severity of ACLF. Type A ACLF is graded as grade AI, AII or AIII, reflecting progressive levels of hepatic dysfunction, and type B ACLF is graded as grade B1, B2 or B3, based on the number of organs with failure. Prospective data collection is needed to validate this classification system across different geographic regions and patient populations.

Prognostic scores for ACLF

As with the definitions of ACLF, prognostic scores for ACLF vary globally. The Model for End-stage Liver Disease (MELD) score is used to assess the severity of CLD and prioritize patients for liver transplantation. A MELD score of >30 generally mandates urgent consideration for liver transplantation[1]. The incorporation of serum sodium level in the modified MELD–Na score helps to identify patients with a low MELD score and hyponatraemia, who have a high risk of mortality[13]. The MELD score does not, however, incorporate parameters such as tissue perfusion (lactate levels), cognitive dysfunction (hepatic encephalopathy) or pulmonary function (ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2 ratio))[14]. The AARC score includes liver failure parameters (bilirubin and INR), hepatic encephalopathy grade, global haemodynamics and tissue perfusion (as indicated by serum lactate levels) and creatinine level to indicate renal status, and hence can be useful for determining a patient's suitability for liver transplantation. The CLIF-C organ failure (OF) score has a range of 6–18 based on the function of six major organ systems (liver, kidney, brain, coagulation, circulatory and respiratory). A higher CLIF-C OF score translates into a higher ACLF grade[7]. The CLIF-C ACLF score is a composite score that integrates the CLIF-C OF score, age and total leukocyte count as components in its calculation to generate a composite score of 0–100 in a linear range; a score of >65 has been shown to predict 80% mortality in 28 days of ACLF diagnosis[15]. However, neither the CLIF-C ACLF score nor the CLIF-C OF score includes serum lactate levels, and hence may be less suitable to assess tissue perfusion and disease severity. Moreover, the CLIF-C OF score often selects patients late and has been validated most often in deceased donor liver transplantation settings[12,15].

The changing spectrum of ACLF aetiologies

Globally, ACLF is commonly reported in patients suffering from alcohol-associated liver disease, metabolic dysfunction-associated steatotic liver disease (MASLD; formerly known as metabolic dysfunction-associated fatty liver disease or non-alcoholic fatty liver disease) and viral hepatitis. The most common acute insults across the Asia–Pacific region are alcohol-associated hepatitis (58%) and hepatitis B virus (HBV) reactivation (13%). The underlying CLD or cirrhosis is predominantly caused by alcohol (67%) followed by MASLD. Similar trends have been reported in Latin America[16] and Japan[9,17]. Many patients have co-existing obesity, diabetes and dyslipidaemia, predisposing them to an increased probability of the failure of organs[18]. In China,

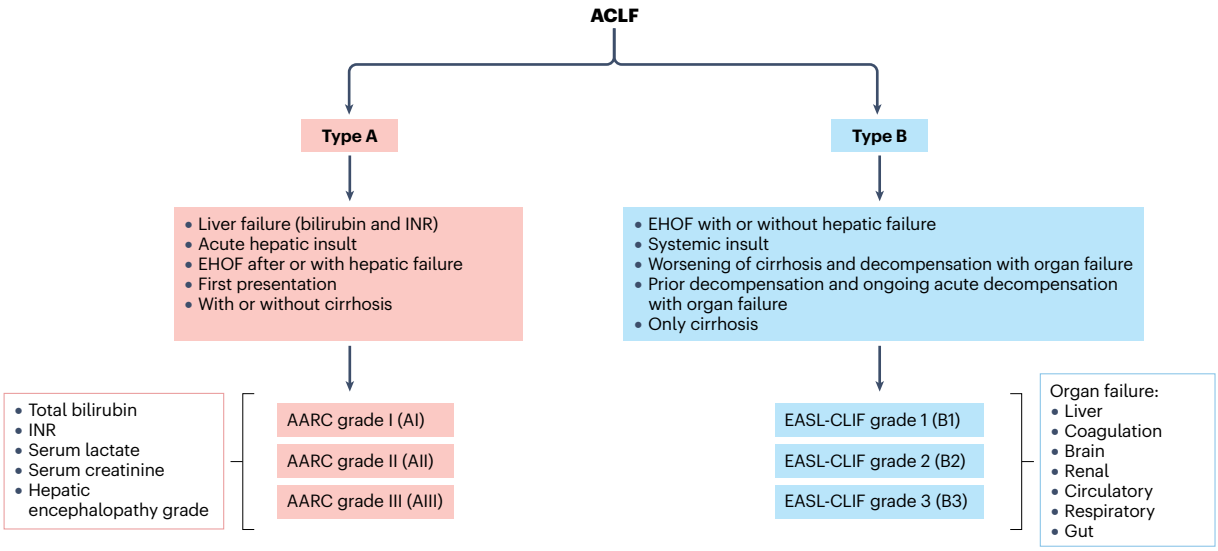


Fig. 2 | Proposed Kyoto classification of acute-on-chronic liver failure and indices for assessment of severity. The acute-on-chronic liver failure (ACLF) definition and indices of severity have been reviewed by global experts[12] with the aim of a global consensus. The Kyoto Consensus proposes that ACLF be classified into two types: type A and type B. Type A is defined as being liver failure dominant at presentation (which aligns with the Asian Pacific Association for the Study of the Liver (APASL) and Japanese definitions). Type A ACLF does not include patients with previous decompensation or extrahepatic insults, it can be reversible and infection is considered to be a consequence of ACLF more often than as a precipitant of ACLF. In type B ACLF (which corresponds with the European Association for the Study of the Liver Chronic Liver Failure consortium (EASL–CLIF) and the North American Consortia for the Study of End Stage Liver Disease definitions), extrahepatic manifestations are predominant at presentation (for example, acute kidney injury, circulatory failure, respiratory failure, coagulopathy or hepatic encephalopathy), often with sepsis or systemic inflammation as the primary driver; liver failure (jaundice or coagulopathy) can be a subsequent presentation in a patient with acute decompensation or further decompensation leading to ACLF. However, type B also includes patients who have liver failure as the first presentation. Liver failure is considered an essential criterion for diagnosis of ACLF in the APASL, the American Association for the Study of the Liver Diseases and the Chinese Group on the Study of Severe Hepatitis B definitions. The Kyoto Consensus also introduced a system to grade the severity of ACLF. Type A ACLF can be graded as per the ACLF Research Consortium (AARC) grading system (with grades I, II and III reflecting progressive levels of hepatic dysfunction) for severity assessment; type A ACLF can occur with or without extrahepatic organ failure (EHOF). Type B ACLF is proposed to be graded as B1, B2 and B3 as per the EASL–CLIF score, based on the number of organs with failure. INR, international normalized ratio.

Central Asia and Africa, HBV remains the most common cause of CLD and cirrhosis, and reactivation of HBV is the most common acute insult responsible for the development of ACLF[19]. Drug-induced liver injury as a cause of acute liver injury is increasing globally[20]. The most commonly involved drugs include antibiotics, anti-epileptics, NSAIDs, anti-tuberculosis drugs, traditional and complementary medicines, herbal and dietary supplements and, more recently, immune checkpoint inhibitors[20,21]. *Polygonum multiflorum* from China and Korea, and Ayurvedic medicines or natural herbs such as *Tinospora cordifolia* (also known as giloy) from India, are reported as causes of ACLF[22–24]. In a prospective cohort of 3,132 patients with ACLF across Asia, drugs were implicated as a cause in 10.5% of cases, of which herbal medications contributed 71.7%, followed by anti-tubercular drugs (27.3%); incident 90-day mortality was 46.5% in drug-induced ACLF and 38.8% in non-drug-induced ACLF[25].

Mechanisms of liver injury and cellular pathology in ACLF

Three major 'battlefields' are interacting in a patient with ACLF at a given time: a severe and acute liver injury inflicted on top of CLD or cirrhosis, the worsening of a pro-inflammatory gut milieu, and immune dysfunction. These three events result in uncontrolled systemic inflammatory, oxidative and metabolic stress leading to immune paresis, sepsis and organ failure (Fig. 3).

Hepatocellular injury as the driver of ACLF

The liver has a central role in the clearance of enteric and systemic pathogens, dying cells and immune complexes to maintain the physiological immune tolerance against damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). This tolerance gets disrupted in cirrhosis, resulting in a condition referred to as cirrhosis-associated immune dysfunction. Cirrhosis-associated immune dysfunction forms the basis of rapid worsening observed in ACLF[26]. In ACLF, immunogenic forms of cell death such as necrosis, necroptosis and pyroptosis, become the prominent forms of cell death, leading to the increased release of DAMPs from injured, dying or dead cells[27,28]. Levels of PAMPs and microbe-associated molecular patterns (MAMPS) are also increased owing to enhanced gut bacterial translocation and infections[29]. The perpetual presence of DAMPs, PAMPs and MAMPs leads to inflammasome-mediated production of cytokines and chemokines that results in the recruitment of neutrophils, monocytes and natural killer cells to the liver[30,31], which leads to further hepatocyte death, and initiates a vicious cycle of immune-mediated hepatocellular injury and cytokine storms.

Hepatocellular injury releases a wide range of DAMPs, including HMGB1, histones, IL-33, IL-1α, IL-17, IL-22, TNF, heat shock proteins and mitochondrial DNA[32]. HMGB1 is a conserved nuclear protein that is present in all cell types. Under stress or upon cell death, HMGB1 translocates to the extracellular region where it acts as an alarmin,

activating innate immunity[33]. DAMPs and PAMPs are recognized by pattern-recognition receptors in the liver (with HMGB1 recognized by RAGE and lipopolysaccharide primarily recognized by Toll-like receptor 4 (TLR4)), which activates the inflammasome to secrete pro-inflammatory cytokines such as IL-1β and IL-1α (which stimulate chemokine production and innate cell activation). IL-1β and IL-1α have both been linked to the development and severity of ACLF, and single nucleotide polymorphisms in genes encoding these cytokines have been reported as being protective against ACLF[34,35].

Inflammatory mediators can stimulate inducible nitric oxide synthase in the splanchnic and systemic vascular endothelium, which results in increased circulating levels of nitric oxide, splanchnic vasodilation and activation of endogenous neurohumoral vasoconstrictor pathways, in turn leading to hypoperfusion and hepatorenal syndrome (HRS)-type acute kidney injury (AKI)[36,37]. Immune mediators released via the TNF signalling pathway and the nuclear factor-κB (NF-κB)-dependent signalling pathway have been associated with circulatory dysfunction and pulmonary ventilation–perfusion mismatch, leading to respiratory failure and a vicious cycle of direct inflammatory tissue damage and further release of cellular products, perpetuating systemic inflammation and organ failure[27,38].

Intestinal bacterial translocation and immune response

Changes in the gut microbiota strongly influence the development and progression of ACLF. Increased gut permeability and transcytosis of bacteria (largely mediated by IL-10) and translocation of gut-derived PAMPs contribute to hepatic and systemic inflammation (Fig. 3). A study showed that cirrhosis is associated with a reduction in gene and metagenomic species richness in the gut microbiome and that it decreases with disease progression, with patients with ACLF having the lowest richness of bacteria[39]. Patients with ACLF had significantly increased levels of pathogenic *Enterococcus* and *Peptostreptococcus* species, and patients with decompensated cirrhosis had increased levels of *Faecalibacterium*, *Ruminococcus* and *Eubacterium* (versus patients with ACLF)[39]. In another study in patients with severe alcohol-associated hepatitis, the phyla Proteobacteria and Fusobacteria were associated with increased long-term mortality, and increased levels of gut bacteria from the Firmicutes phylum, the Lachnospiraceae family, and *Veillonella* and *Prevotella* genera were shown to favour survival[40]. Although increased abundance of Prevotellaceae and Pasteurellaceae have been associated with increased mortality in HBV-related ACLF[41], reduced abundance of *Akkermansia muciniphila* is seen in severe alcohol-associated hepatitis[40,42]. Carbapenem-resistant gram-negative bacteria were isolated from the stool of 42% of hospitalized patients with ACLF, and were strongly associated with development of infectious complications (relative risk (RR) 5.5; $P < 0.001$)[31]. Fungal dysbiosis, high levels of exotoxins (for example, candidalysin and cytolysin) and an altered virome have been reported in patients with ACLF[43]. The intestinal microbiota and bile acids have a bidirectional relationship: the bacteria are involved in the metabolism of bile acids and can modify isomerization of bile acids into secondary bile acids, which influences the intestinal microbiota composition, while the bile acids have antimicrobial effects and can module signalling pathways that can shape the gut microbiome[41]. Dysbiosis of the gut microbiota affects conversion of primary to secondary bile acids by bile salt hydrolase, alters the pH of the intestine, has toxic effects and affects activity of Farnesoid X receptor. An increase in secondary bile acids, a reduction in primary bile acids and a reduction in bacteria producing short-chain fatty acids contribute to the pathogenesis of ACLF[44].

Bio-energetic dysfunction in ACLF: sepsis and organ failure

An intricate balance between 'disease resistance' (a mechanism by which the immune system recognizes, attacks and eliminates or blocks the invasion of pathogens) and 'disease tolerance' (a defence mechanism of the host to limit the infection or immune-mediated tissue damage) is critical for homeostasis[45]. Maintaining this balance requires coordination between pathways involved in the metabolism of glucose, amino acids and one-carbon metabolism; these pathways converge in mitochondria, which act as the cellular energy hub (Fig. 3). In ACLF, a metabolic shift occurs where glucose is used preferentially by cells for anabolic processes (through increased cytosolic aerobic glycolysis and the pentose phosphate pathway) rather than for generating ATP through mitochondrial pathways[45–47]. Non-essential amino acids and the one-carbon metabolism network are also involved in the anabolism of proteins, nucleotides and lipids to support leukocyte proliferation[45,48]. Patients with ACLF often have low dietary intake, partly related to inflammation-induced anorexia. The body redirects nutrients from liver glycogenolysis and skeletal muscle proteolysis to support the high metabolic demand of the activated innate immune system at the expense of peripheral organs, shifting them towards a 'dormancy programme' which could lead to reduced effective tissue perfusion and contribute to organ failure[49]. Furthermore, aggravated systemic inflammatory responses induce suppression of mitochondrial respiration, which is required for bacterial phagocytosis[50]. In patients with ACLF, monocytes show an increase in the expression of genes related to glycolysis and a decrease in genes associated with oxidative phosphorylation (OXPHOS); despite the differences in gene expression, notable impairments occur in both glycolysis and OXPHOS activity in these monocytes, which leads to reduced oxidative burst and impaired phagocytic function[50,51]. In a small study, patients with ACLF who had monocytes with a maximum mitochondrial respiration of <37.9 pmol/min or baseline glycolysis of ≤42.7 mpH/min showed increased 28-day mortality ($P < 0.001$). Monocyte function could partly be restored by mitochondrial transfer using umbilical cord mesenchymal stem cell (MSC) therapy[50].

Four differentially expressed genes have been shown to be involved in the immune–metabolic disorder that contributes to the initiation and development of ACLF in patients with chronic HBV infection: thrombospondin 1 (increased expression), MERT-K (increased expression), semaphorin 6B (increased expression) and PPARγ (minimal expression)[52]. Increased hepatocyte apoptosis and high levels of IL-33 and its receptor ST2 (a member of the TLR superfamily) are also associated with ACLF[53].

In summary, hepatocellular injury in ACLF is driven by an altered metabolic milieu, immune cell dysfunction and bioenergetic failure, reflecting a hyperactive but functionally impaired immune system with a notable reduction in antigen presentation and upregulation of inhibitory molecules. Metabolic dysregulation is central to the dysregulation of immune cells, which leads to a sepsis-like immunological state that contributes to the increased susceptibility to infections seen in patients with ACLF[45,54,55].

Innate immune response

Monocytes and macrophages. Monocytes and macrophages are the first line of defence against invading pathogens and have a central role in both the progression and resolution of liver injury. In healthy livers, the liver macrophage pool is maintained by the self-renewal of resident embryonic Kupffer cells; during liver injury, the Kupffer cell pool is supplemented by bone-marrow-derived macrophages (BMDMs)[56].

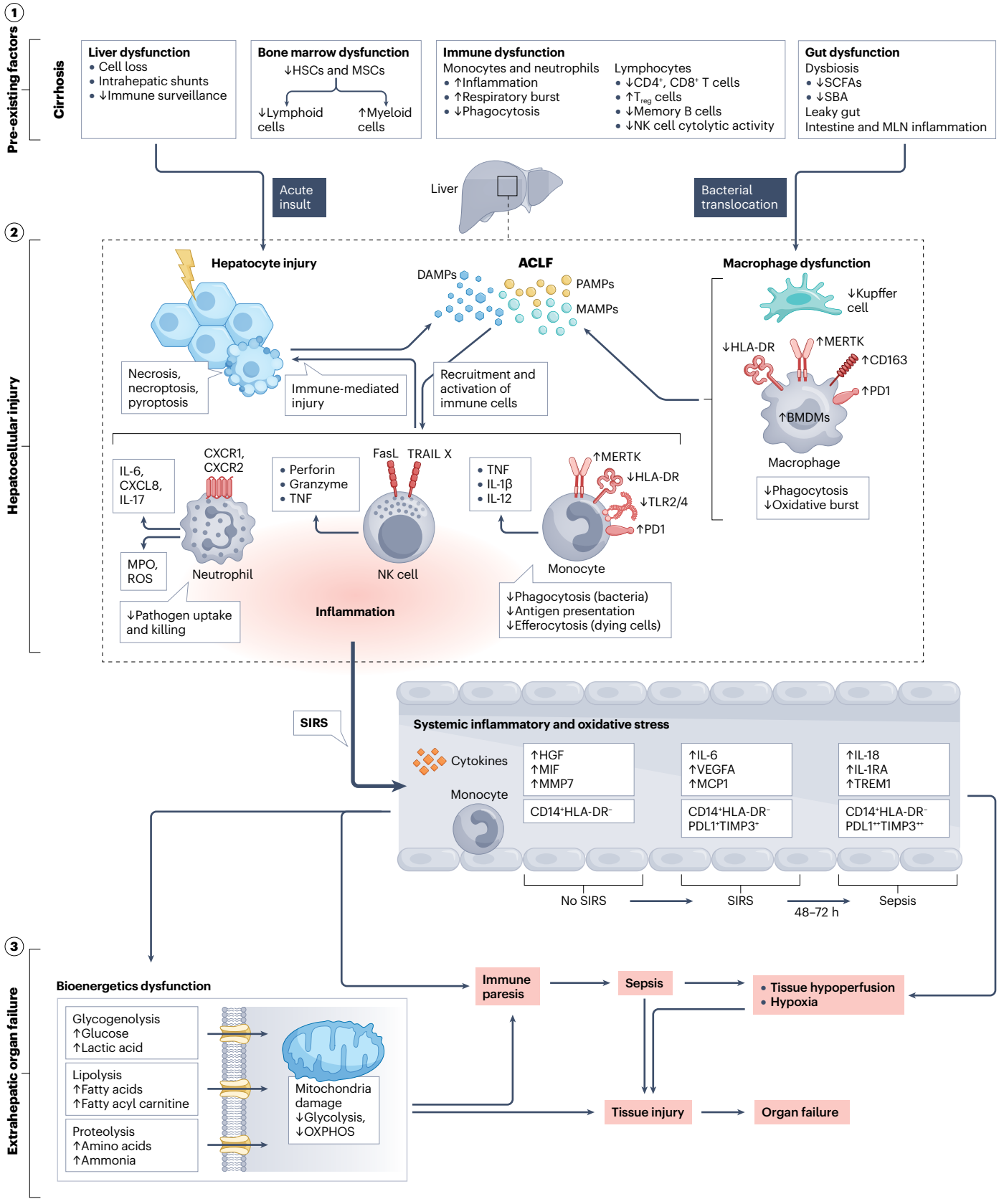

1
Pre-existing factors
Cirrhosis
Liver dysfunction
• Cell loss
• Intrahepatic shunts
• ↓Immune surveillance
Bone marrow dysfunction
↓HSCs and MSCs
↓Lymphoid cells
↑Myeloid cells
Immune dysfunction
Monocytes and neutrophils
• ↑Inflammation
• ↑Respiratory burst
• ↓Phagocytosis
Lymphocytes
• ↓CD4+, CD8+ T cells
• ↑Treg cells
• ↓Memory B cells
• ↓NK cell cytolytic activity
Gut dysfunction
Dysbiosis
• ↓SCFAs
• ↓SBA
Leaky gut
Intestine and MLN inflammation
Acute insult
Liver
Bacterial translocation
2
Hepatocellular injury
Hepatocyte injury
Necrosis, necroptosis, pyroptosis
Immune-mediated injury
DAMPs
ACLF
PAMPs
MAMPs
Recruitment and activation of immune cells
Macrophage dysfunction
↓Kupffer cell
↓HLA-DR
↑MERTK
↑CD163
↑PD1
↑BMDMs
Macrophage
↓Phagocytosis
↓Oxidative burst
IL-6, CXCL8, IL-17
CXCR1, CXCR2
MPO, ROS
Neutrophil
↓Pathogen uptake and killing
• Perforin
• Granzyme
• TNF
FasL
TRAIL X
NK cell
• TNF
• IL-1β
• IL-12
↑MERTK
↓HLA-DR
↓TLR2/4
↑PD1
Monocyte
↓Phagocytosis (bacteria)
↓Antigen presentation
↓Efferocytosis (dying cells)
Inflammation
SIRS
Systemic inflammatory and oxidative stress
Cytokines
Monocyte
↑HGF
↑MIF
↑MMP7
CD14+HLA-DR−
↑IL-6
↑VEGFA
↑MCP1
CD14+HLA-DR−
PDL1+TIMP3+
↑IL-18
↑IL-1RA
↑TREM1
CD14+HLA-DR−
PDL1++TIMP3++
No SIRS
SIRS
48–72 h
Sepsis
3
Extrahepatic organ failure
Bioenergetics dysfunction
Glycogenolysis
↑Glucose
↑Lactic acid
Lipolysis
↑Fatty acids
↑Fatty acyl carnitine
Proteolysis
↑Amino acids
↑Ammonia
Mitochondria damage
↓Glycolysis,
↓OXPHOS
Immune paresis
Sepsis
• Tissue hypoperfusion
• Hypoxia
Tissue injury
Organ failure

Fig. 3 | Pathophysiology of acute-on-chronic liver failure. Three major factors contribute to the pathophysiology of acute-on-chronic liver failure (ACLF): pre-existing cirrhosis associated dysfunction[1], immune-mediated hepatocellular injury[2], and systemic inflammation-induced immune paresis, sepsis and secondary organ dysfunction and/or failure[3]. The specific contribution of each factor varies between patients, and these factors interact with each other and contribute to the complex development of ACLF in a given patient[1]. In pre-existing cirrhosis-associated dysfunction (1), liver cirrhosis is commonly associated with poor liver immune surveillance (owing to loss of parenchymal and non-parenchymal mass and development of intrahepatic shunts), cirrhosis-associated immune cell dysfunction, loss of bone marrow stem cell reserve, increased enteric bacterial translocation to liver (owing to gut dysbiosis, leaky gut, intestine and mesenteric lymph node inflammation, impaired intestinal motility and reduced gastric acidity) that leads to low-grade systemic inflammation, immune exhaustion and loss of physiological immune tolerance against damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). The degree of these pre-existing cirrhosis-associated dysfunctions majorly contributes to ACLF injury and outcome[2]. In immune-mediated hepatocellular injury in ACLF (2), immunogenic forms of cell death such as necrosis, necroptosis, and pyroptosis, are more prominent than cirrhosis, which leads to increased release of DAMPs. Further, owing to infections, enhanced gut bacterial translocation and failure of the liver macrophage-mediated gut–liver barrier markedly increase the PAMPs and microbe-associated molecular patterns (MAMPs). The perpetual presence of these DAMPs, PAMPs and MAMPs leads to inflammasome-mediated production of cytokine and chemokines, which results in the recruitment of neutrophils, monocytes and natural killer (NK) cells to the liver that further aggravates the hepatocyte death and initiates the vicious cycle of immune-mediated hepatocellular injury and cytokine storms[3]. In systemic inflammation-induced immune paresis, sepsis and secondary organ dysfunction or failure, the increased systemic inflammatory response (owing to cytokine storms, DAMPs, PAMPs, MAMPs and activated immune cells) together with reduced disease tolerance (owing to metabolic dysfunction, mitochondrial damage and bio-energy failure) can cause immune paresis and sepsis. Collateral damage to extrahepatic tissues also occurs (3), leading to secondary organ dysfunction or failure. BMDMs, bone-marrow-derived macrophages; CXCL8, CXC-chemokine ligand 8; FasL, Fas ligand; HGF, hepatocyte growth factor; HSC, haematopoietic stem cell; MCP1, monocyte chemoattractant protein 1; MIF, macrophage migration inhibitory factor; MLN, mesenteric lymph node; MMP, matrix metalloproteinase; MPO, myeloperoxidase; MSC, mesenchymal stem cell; OXPHOS, oxidative phosphorylation; PD1, programmed cell death 1; PDL1, programmed cell death 1 ligand 1; ROS, reactive oxygen species; SBA, secondary bile acid; SCFA, short-chain fatty acid; SIRS, systemic inflammatory response syndrome; TIMP3, tissue inhibitor of metalloproteinase 3; T_{reg} cell, regulatory T cell; VEGFA, vascular endothelial growth factor A.

In patients with ACLF, although numbers of monocytes (in the peripheral blood and liver) and macrophages (in the liver) are increased compared with numbers in patients with compensated cirrhosis, these cells are functionally impaired owing to mitochondrial dysfunction and bio-energetic failure akin to sepsis[50,55]. The monocytes show reduced expression of TLR2, TLR4 and HLA-DR, which compromises TLR-elicited responses to microbial challenges[51]. The expansion of $CD14^+HLA\text{-}DR^-$ myeloid-derived suppressor cells leads to decreased T cell proliferation, which results in impaired adaptive immune responses against infection[57]. High and rising levels of plasma IL-1RA, IL-18 and TREM1 soluble factors, and increased suppressive monocytes ($PDL1^+TIMP3^+$) at baseline in patients with ACLF have been shown to predict a high risk of developing sepsis within 48 h of hospitalization[58]. Increased levels of monocyte-derived extracellular vesicles are seen in patients with ACLF, impairing monocyte function and leading to increased inflammation and mortality[59,60]. In patients with ACLF, monocytes show defective efferocytosis (the process of clearance of dying immune cells and hepatocytes) which leads to increased inflammation[61,62]. Studies have shown that macrophage dysfunction in ACLF is initiated by fungal peptides and specific lipid molecules[63]. Survivors of ACLF exhibit a monocyte transcriptome that is enriched with anti-inflammatory genes such as resistin (which prevents excess inflammation to lipopolysaccharide) and alarmins (which makes monocytes less responsive to TLR4 stimulation) suggesting a shift towards immune tolerance[64].

Neutrophils. Neutrophils are a key part of the first line of defence of the innate immune system and are recruited to sites of infection to eliminate pathogens. Neutrophils are increased in patients with ACLF with higher expression of CXC-chemokine receptor 1 (CXCR1) and CXCR2 (needed for chemotaxis) and increased levels of CXC-chemokine ligand 8 (CXCL8) and IL-8 ligands, correlating with hepatocellular injury and mortality[29]. Elevated neutrophil-to-lymphocyte ratio is a prognostic indicator of poor survival in patients with ACLF[65]. In ACLF, neutrophils show increased release of reactive oxygen species (ROS), increased migration to hepatocytes, and diminished phagocytic capacity, possibly owing to dysregulation in the NADPH oxidase complex[66]. In ACLF, neutrophils show increased capacity to form neutrophil extracellular traps, the formation of which is promoted by pyroptosis, glycolysis and high fibrinogen-like protein 2 (FGL2) expression[66–68]. In alcohol-associated ACLF, increased conversion of bilirubin to urobilinogen by gut microbiota promotes neutrophil activation[69]. This process increases low-density neutrophils, a mature exhausted phenotype that has reduced ability to perform its normal functions[70]. Agonists of TLR7 and TLR8 (ref. 71) and granulocyte colony-stimulating factor (GCSF)[72] can improve neutrophil count and function; in fact, GCSF has been successfully used for immune modulation and treatment of patients with ACLF[72].

Adaptive immune response: lymphocytes

Dysregulation of the adaptive immune response occurs relatively early during chronic liver injury and precedes ACLF[73]. In patients with acute decompensation and patients with ACLF, numbers of circulating $CD4^+$ and $CD8^+$ T cells are reduced and show an immune-suppressive phenotype[74]. Patients with ACLF also show a reduced fraction of naive B cells in both the blood and the liver as well as an increased percentage of antigen-experienced B cells, including activated memory B cells, atypical memory B cells and age-associated B cells compared with patients with cirrhosis and healthy controls[75]. The precise relevance of the phenotypic changes in the B cell compartment in ACLF is not well understood.

Albumin dysfunction and inflammation in ACLF

In healthy individuals, serum albumin exists in three major isoforms: the reduced form known as human mercaptalbumin (70–80%), the reversibly oxidized form known as human non-mercaptalbumin 1 (HNA1; 20–25%), and the irreversibly oxidized form known as HNA2 (5%)[76]. In patients with ACLF, oxidized forms of albumin are increased and activate neutrophils leading to their degranulation, release of ROS and progression of alcoholic hepatitis[77]. HNA2 makes the platelets in ACLF pro-inflammatory and could thereby contribute to organ injury. HNA2 levels of >12% have been shown to correlate with high 1-month mortality in patients with decompensated cirrhosis[78]. Hyperbilirubinaemia in

ACLF leads to one albumin molecule binding to many bilirubin molecules, preventing binding of other ligands and allowing high circulatory levels of toxic metabolites[76] (Supplementary Fig. 1).

Clinical course of ACLF

Clinical components of ACLF

ACLF is characterized by a sudden worsening of liver function in an individual with pre-existing CLD. ACLF is marked by liver failure (jaundice, coagulopathy and/or hepatic encephalopathy and associated complications), evidence of CLD with or without cirrhosis and development of acute portal hypertension (identified as occurrence of ascites, varices or variceal bleeding)[12]. The natural history of ACLF involves the initial insult and its effect on the liver, and the events triggered by the original insult, as shown by EHOFs. An understanding of both of these aspects is crucial for the diagnosis and effective management of ACLF[79]. Knowledge of the stage of the underlying CLD or cirrhosis is also important as it indicates the underlying hepatic reserve and state of pre-existing portal hypertension[80].

Acute portal hypertension

During ACLF in patients with cirrhosis and pre-existing portal hypertension, an acute rise in portal pressure occurs, driven by hypercytokinaemia, elevated bile acids and bilirubin, stellate cell overactivation, endothelial dysfunction and impaired vasorelaxation[81]. The sudden rise in portal hypertension can lead to rapid development of ascites, increased risk of variceal bleed, organ failure(s) and reduced survival[81]. A prospective study conducted from 2008 to 2011 enrolled 57 patients with ACLF who underwent baseline hepatic venous pressure gradient (HVPG) measurement, which indirectly reflects portal pressure. Baseline HVPG was higher in those who died than in those who survived (median 21 mmHg (range 13.5–32 mmHg) versus 15 mmHg (range 9.5–30 mmHg), respectively; $P < 0.05$). Among the 31 survivors, 24 of whom agreed to a repeat HVPG measurement, median HVPG reduced from 16 to 13 mmHg during 3 months of follow-up[82]. Patients with ACLF have a higher HVPG than patients with cirrhosis, with increased systemic and pulmonary vasodilation (the pulmonary bed dilation being more dominant)[83]. Use of carvedilol ($n = 66$) to reduce portal pressure was found to reduce AKI, systolic blood pressure (SBP) and 28-day mortality compared with placebo ($n = 70$) in a randomized controlled trial (RCT) ($P < 0.044$)[84].

In another large study ($n = 4,434$), patients with ACLF who presented with acute variceal bleeding ($n = 72$) had a higher baseline HVPG than patients without acute variceal bleeding (median 25 mmHg versus 17 mmHg; $P < 0.045$) and acute variceal bleeding was associated with increased 6-week mortality[85]. In many patients with ACLF, the raised portal pressure reduces with resolution of hepatocellular injury and ACLF syndrome[10].

Ascites is a defining component of ACLF and was found in 91% of patients at admission in the APASL cohort[1]. Ascites presents differently in patients with ACLF and in patients with decompensated cirrhosis, with ACLF-related ascites having a more acute onset, less pronounced flank fullness, increased intra-abdominal pressure and an increased incidence of diuretic intolerance[79,86]. Owing to the underlying severe inflammation, the abdomen can appear tense even with a small amount of fluid, with tenderness and mild guarding occurring even without a bacterial infection, a condition sometimes referred to as 'inflammatory ascites'[86,87].

Organ failure in ACLF

Assessing organ dysfunction and organ failure. Assessing degrees of organ dysfunction and organ failure is crucial for evaluating the severity (Fig. 4), progression and urgency for liver transplantation in patients with ACLF[1]. Hepatic dysfunction and failure are primarily evaluated through rapid rises in serum bilirubin and INR, with or without the development of hepatic encephalopathy[1,12,88]. Lactate levels also reflect the severity of liver and metabolic failure and are used in the AARC score (which includes four parameters of liver failure including lactate and serum creatinine to predict severity) and the MELD–lactate scoring system (the MELD score is used to assess the severity of CLD and prioritize patients for liver transplantation, and the addition of

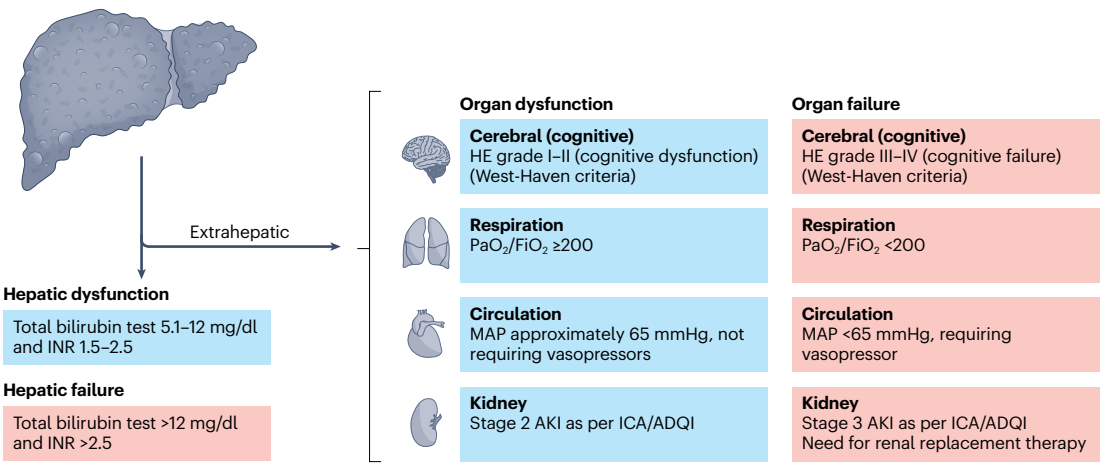


Fig. 4 | Suggested definitions of organ dysfunction and organ failure in acute-on-chronic liver failure according to the Kyoto Consensus. During organ dysfunction, efforts should focus on recovery and prevention of progression to organ failure. Definitions of hepatic failure consider both coagulation (with an international normalized ratio (INR) of 1.5–2.5 considered as coagulation dysfunction and an INR of >2.5 considered as coagulation failure) and jaundice (as determined by bilirubin level). Suggested definitions of dysfunction and failure of extrahepatic organs (cerebral, renal, circulatory and respiratory) are also shown. The cut-off values have been published in the Kyoto Consensus[12]. ADQI, Acute Disease Quality Initiative; AKI, acute kidney injury; HE, hepatic encephalopathy; ICA, International Club of Ascites; MAP, mean arterial pressure. Adapted from ref. 12, Springer Nature Limited.

lactate can improve mortality prediction, especially in critically ill cirrhotic patients)[89,90]. The EASL–CLIF definitions of organ failure are primarily based on the sequential organ failure assessment (SOFA) score[7,91] which numerically quantifies the number and severity of failed organs, and was developed to assess and monitor organ dysfunction at a population level (not an individual level) in critically ill patients with sepsis and bloodstream infections. Recognizing and categorizing organ dysfunction separately from failure is important for monitoring response to therapy and to give insights into prognosis[92].

Prevention of ACLF and organ failure. Preventing ACLF and organ failure is complex and requires targeted interventions tailored to specific geographical regions owing to variations in prevalent causes and risk factors. Strategies include targeting the downstream effects of toxic metabolites and systemic inflammation, and manipulating the gut microbiome with rifaximin or non-antibiotic gut decontaminating treatments[93]. COSSH developed a prognostic score for the onset of ACLF (using total bilirubin, INR, alanine transaminase and ferritin values) to predict acute deterioration of HBV-related CLD. Patients with a score of ≥6.3 were at high risk of developing ACLF[93]. Several new metabolic biomarkers have been identified and high baseline plasma 11-deoxycorticosterone levels have been shown to correlate with early mortality in patients with ACLF[94,95]. High serum ferritin and increased labile iron pool in macrophages have been shown to predict organ failure and mortality in patients with ACLF[96]. Single-cell sequencing and multiomics are enabling the identification of new biomarkers and, together with machine learning tools, could help to identify patients at risk of developing ACLF[97,98].

From SIRS to organ failure in ACLF. Acute hepatic insult in a cirrhotic liver hyperactivates the immune response to a pathological cellular and cytokine milieu that aims to restrict the ongoing injury. The clinical manifestation of such an inflammatory state is known as systemic inflammatory response syndrome (SIRS). Clinical assessment of SIRS can be challenging in patients with ACLF who are on non-selective beta blockers (NSBBs) or have ascites, as NSBBs reduce heart rate and ascites can cause tachypnoea, both of which are key components of SIRS. A large prospective study monitored 561 consecutive patients with ACLF for the development of SIRS or sepsis and associated complications and followed them for 90 days[88]. Of these 561 patients, 201 (35.8%) had no SIRS and 360 (64.2%) had SIRS with or without infection. New-onset SIRS developed in 74.6% of patients and sepsis developed in 8% of patients at a median of 7 days (range 4–15 days), at a rate of 11% per day. The absence of SIRS in the first week was associated with a reduced incidence of organ failure (20% versus 39.4%; $P = 0.003$) and reduced 28-day mortality (17.6% versus 36%; $P = 0.02$). The results suggest the concept of a 'golden window' in the first week after diagnosis, a period during which prompt interventions might improve patient outcomes[12,88,99].

Immune paresis and development of infection and sepsis. The immune system is severely compromised in patients with cirrhosis, and bacterial and fungal infections are frequent in patients with ACLF[88,100]. Different stages and patterns of host inflammatory responses, SIRS, compensatory anti-inflammatory response syndrome and mixed antagonistic response syndrome reflect the host response to infections and outcomes in patients with ACLF[2]. Biomarkers such as procalcitonin, C-reactive protein, TNF, IL-2 and IL-6, can help detect and monitor stages of bacterial infection[1,6,101]. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry and next-generation metagenomic sequencing are more helpful for early pathogen identification than traditional bacterial culture methods[102–104]. For diagnosis and monitoring of fungal infections, galactomannan and (1,3)-β-D-glucan tests are helpful[105]. Use of point-of-care multiplex PCR based systems can help identify pathogens and monitor stages of infection, enabling selection of appropriate antimicrobial agents[1,6,101]. The prevention of hospital-acquired infections and 'second-hit events' (acute insults that trigger further worsening of the patient's condition) is vital for improving survival in patients with ACLF[100].

Kidney dysfunction and failure. Kidney dysfunction is present in about one-third of patients at the time of ACLF diagnosis[6,106,107]. New-onset AKI is also common, demonstrating that renal reserve is limited in these patients. AKI in a patient with ACLF is different from AKI in a patient with decompensated cirrhosis, with ACLF-related AKI being associated with increased and more rapid structural damage to the kidneys and being less responsive to terlipressin[108]. High levels of serum bile acids, renal ischaemia and sepsis contribute to tubular epithelial cell and endothelial cell injury, causing apoptosis, and contributing to the pathogenesis of AKI in ACLF[106]. Patients with ACLF who develop AKI are more likely to have non-resolution of AKI and progression of AKI than patients without ACLF[108]. Biomarkers such as urinary neutrophil gelatinase-associated lipocidin and cystatin C are used to predict and assess AKI in decompensated cirrhosis, but have not been adequately evaluated in ACLF[106]. Instead, in patients with ACLF a rise in serum creatinine of 0.3 mg/dl, even at levels >0.7 mg/dl, as in the AARC score, should be taken seriously as it could indicate progression of ACLF grade[1,88].

The management of AKI in patients with ACLF requires a proactive approach to preserve kidney function. To reduce the risk of AKI, adequate blood pressure should be maintained (as hypotension can lead to AKI), nephrotoxic drugs such as NSAIDs, amphotericin and colistin should be minimized or avoided as should unnecessary intravenous contrast studies. For patients with HRS-type AKI, terlipressin alone or in combination with noradrenaline is considered effective[106]. In a study comparing albumin plus terlipressin infusion or albumin plus noradrenaline infusion, terlipressin infusion demonstrated superiority over noradrenaline infusion (reversal of HRS occurred in 40% versus 16.7% of patients; $P = 0.004$)[109]. In a subset analysis of the CONFIRM study, a randomized, placebo-controlled trial investigating terlipressin in patients with HRS, terlipressin was associated with a shorter intensive care unit stay and improved renal function in patients with cirrhosis and HRS[110]. As renal injury is often rapidly progressive in patients with ACLF, terlipressin should be introduced early: the eTerli trial showed that infusion at 12 h instead of 48 h from onset was associated with reduced short-term mortality, early AKI reversal and regression of ACLF stage[111]. The APASL clinical practice guidelines suggest that vasoconstrictors should be initiated early in patients with ACLF and HRS-type AKI[12,106].

Cognitive dysfunction and failure in ACLF. Hepatic encephalopathy is the most common form of cognitive dysfunction in ACLF, occurring in 20–40% of patients with ACLF, and is associated with high mortality rates[112]. The West Haven scale can be used to grade the severity of hepatic encephalopathy, with grades I and II indicating cerebral (cognitive) dysfunction, and grades III and IV indicating cerebral (cognitive) failure[113] (Fig. 4). The pathophysiology of hepatic encephalopathy in ACLF is multifactorial, with cerebral energy impairment, hyperammonaemia, infection and SIRS all being involved[114]. Intracranial

hypertension and cerebral oedema are uncommon but sometimes occur in ACLF[114].

Management of hepatic encephalopathy focuses on treating precipitating factors such as infections, gastrointestinal bleeding, electrolyte imbalances, constipation and hypovolaemia, discontinuing diuretics (which can precipitate hepatic encephalopathy), reducing ammonia levels using lactulose or polyethylene glycol and addressing systemic inflammation. For refractory hepatic encephalopathy, extracorporeal liver support systems and plasma exchange can help to lower ammonia levels and provide symptomatic relief, but without clear survival advantage[115,116].

Coagulation disorders in ACLF. In patients with ACLF, the coagulation system shuffles delicately between hypocoagulation and hypercoagulation, depending on the disease stage, infections and administered drugs. Prothrombin time (PT)-derived INR measures activity of procoagulant factors but does not show changes in anticoagulants and therefore does not predict bleeding risk in patients with cirrhosis[117]. Viscoelastic testing methods such as thromboelastography and rotational thromboelastometry (ROTEM) are preferred as they provide functional evaluation of procoagulant and anticoagulant pathways, platelet function and hyperfibrinolysis[118]. In a prospective study involving 243 patients with ACLF, a hypocoagulable state at baseline (as measured by thromboelastography) was associated with an increased risk of bleeding (HR 2.1; $P = 0.050$) and increased mortality (HR 1.9; $P = 0.043$)[119]. Furthermore, protein C activity <30% (HR 1.3; $P = 0.042$) and tissue plasminogen activator >20 ng/ml (HR 1.2; $P = 0.040$) were predictors of mortality at day 28. In patients with ACLF, prolonged time to initial fibrin formation prolonged clot formation time and reduced clot firmness are associated with increased short-term mortality[119,120]. Injudicious use of albumin, antibiotics and antifungals can worsen coagulopathy[121]. Routine correction of coagulopathy is unwarranted and should be guided by thromboelastography or ROTEM findings, with cryoprecipitate being useful for hypofibrinogenaemia and four-factor prothrombin complex concentrate being useful for reversing anticoagulation or managing major bleeding[122].

Circulatory and respiratory dysfunction and failure. Circulatory dysfunction is characterized by a mean arterial pressure (MAP) of around 65 mmHg without the use of vasopressors[12,92]. Patients with circulatory failure require vasopressors to maintain a MAP of ≥65 mmHg[12]. Progression to circulatory failure results in inadequate tissue oxygenation and a rise in serum lactate levels. Persistent hyperlactataemia correlates with increased in-hospital mortality and unfavourable post-transplantation outcomes in patients with ACLF[89].

Respiratory dysfunction is defined by the need for non-invasive oxygen support, with a PaO_2/FiO_2 ratio of ≥200. Respiratory failure is considered when mechanical ventilation is required and/or the PaO_2/FiO_2 ratio is <200. Respiratory failure is associated with high mortality and unfavourable post-transplantation outcomes[123]. Preventing respiratory failure in patients with ACLF involves avoiding positive fluid balance and cautious use of albumin[124].

Gastrointestinal failure. Gastrointestinal failure is often overlooked in patients with critical illnesses[125]. In patients with ACLF, factors that can contribute to gastrointestinal failure include splanchnic vasodilation, lymphatic dysfunction, infections, gut dysbiosis, vasoactive drugs and enemas[126]. Gastrointestinal failure can be indicated by intolerance to enteral nutrition[127], increased gastric residual volume, increased intra-abdominal pressure (of >20 mm of water) and intestinal pseudo-obstruction on imaging.

Managing gastrointestinal failure is challenging. The following approaches might help: positioning the patient to a bed angle of 30°, correction of hypotension, avoidance of lactulose, treating infections, treating spontaneous bacterial peritonitis, managing electrolyte imbalance, post-pyloric feeding, trophic feeding and parenteral feeding[127]. Prokinetic agents such as metoclopramide and intravenous erythromycin have shown some success in improving short-term survival in critically ill patients with cirrhosis[128]. Neostigmine has also been used with limited success for acute colonic pseudo-obstruction[129], but its safety and efficacy in ACLF is anecdotal.

Management of ACLF

Broad principles of management

Patients diagnosed with ACLF are typically sick and can rapidly deteriorate. Assessment using disease severity scores, presence of organ dysfunction or failure, need for hospitalization or intensive care unit monitoring and need for liver transplantation should be done within 72 h of admission[12].

General measures

Nutrition. Nutritional assessment and support is an essential component of the care of patients with ACLF. The Nutrition Risk in the Critically Ill (NUTRIC) score and a non-contrast CT scan at the L3 vertebra can be used to assess sarcopenia, and indirect calorimetry can provide an accurate measure of energy expenditure[12,130]. Myosteatosis and sarcopenia are common in patients with ACLF[131,132] and enteral nutrition with a target daily intake of 30–35 kcal/kg and 1.2–1.5 g protein/kg body weight is recommended[12]. In patients with shock requiring high doses of vasopressors, parenteral ω-3 fatty acids are helpful as they reduce endotoxaemia and inflammation[133]. Enteral nutritional supplementation through a nasogastric tube is advised when the target is not achieved. Adding branched-chain amino acids and ammonia-lowering therapies such as L-ornithine L-aspartate have shown little benefit to nutrition or hepatic encephalopathy prevention[10]. Thiamine or zinc supplements and a late-evening snack can help to improve nutritional status of patients with ACLF[134].

Intensive care in ACLF. Effective intensive care management for patients with ACLF focuses on preventing new infections and failure of organs, managing existing organ dysfunction, and optimizing patients for the potential reversal of ACLF or early liver transplantation. Empirical high-end antibiotic administration at admission upon clinical suspicion of sepsis (while waiting for culture sensitivity reports) and subsequent de-escalation together with antifungals can improve 28-day and 90-day survival in patients with ACLF[135].

Fluid resuscitation with 5% albumin is superior to fluid resuscitation with normal saline in reversing sepsis-related hypotension in critically ill patients with cirrhosis, as shown in the FRISC study, a prospective, open-label, RCT[136]. Use of 20% albumin for fluid resuscitation was associated with faster achievement of a MAP of >65 mmHg and faster reversal of shock, but without survival benefits and with an increased risk of pulmonary complications[137]. In patients who remain hypotensive despite fluid and albumin resuscitation, noradrenaline is recommended as the first-line vasopressor, and should be used within the first 1–3 h of circulatory failure; low-dose vasopressin can be added as a second-line agent to further support blood pressure[124].

Respiratory failure might necessitate the use of a high-flow nasal cannula, non-invasive ventilation, or mechanical ventilation. Fluid overload must be avoided (by using point-of-care ultrasonography to measure the distensibility of the inferior vena cava), and other cirrhosis-specific complications such as hepatic hydrothorax, hepatopulmonary syndrome, portopulmonary hypertension and high intra-abdominal pressure caused by tense ascites should be treated[138]. Patients with ACLF can also develop acute respiratory distress syndrome from direct lung injury (for example, pneumonia) or the sequelae of systemic inflammation, and will require multidisciplinary management.

Therapeutic role of albumin in ACLF. Limited data exists on the benefits and risks of infusion of human albumin solutions in patients with ACLF. Albumin should be administered cautiously in patients with ACLF as it can increase the pre-load on the heart (and lead to congestive heart failure or pulmonary oedema), cause accumulation of fluid into a body's 'third space' (which is neither intracellular nor intravascular) and increase the endogenous pool of dysfunctional albumin[77]. Albumin isoforms, particularly nitroso-albumin, can cause vasodilation and contribute to coagulopathy. Albumin infusion in ACLF is indicated in patients who are undergoing modest-volume paracentesis (MVP) (to prevent paracentesis-induced circulatory dysfunction (PICD)), in patients with SBP and during the initial 3–6 h of septic shock[87]. Limited evidence exists to suggest that medium-term or long-term albumin infusion is safe or alters the natural history of ACLF[139].

Management of portal hypertension. Reducing the rapid rise in portal pressure is a logical approach in the management of patients with ACLF and can be achieved in a number of ways.

Data from a subgroup of the CANONIC study showed that patients with ACLF who continued on NSBBs had lower grades of ACLF at presentation, reduced inflammation, higher resolution (complete or partial) and reduced short-term mortality than those not taking NSBBs[140]. In a randomized trial in patients with ACLF with HVPG of >12 mmHg, and either no varices or small varices, the NSBB carvedilol reduced 28-day mortality, with reduced variceal progression, AKI and SBP development compared with placebo[84]. However, only one quarter of patients with ACLF are eligible for NSBB therapy, as it is not well tolerated owing to the presence of hypotension, circulatory dysfunction, ascites or AKI[141]. Although carvedilol reduces portal pressure more effectively than propranolol and nadolol, it is also associated with greater reduction in blood pressure[142]; studies using propranolol and nadolol are needed in ACLF cohorts.

Midodrine, an oral α_1-adrenergic agonist, has been reported to be safe and beneficial in patients with ACLF as it increases MAP by constricting blood vessels. An increase in MAP of 8.5 mmHg with midodrine has been shown to be associated with a >20% reduction in HVPG[143]. The addition of midodrine might facilitate the use of adequate dose of NSBBs, while preserving renal perfusion[144]. By raising MAP, midodrine also helps to increase tolerability to diuretics and improves ascites control and reduces the incidence of PICD[145].

Endoscopic band ligation (EBL) for prevention of first variceal bleed in patients of ACLF is a contentious issue. EBL, a procedure that uses elastic bands to obliterate varices in the oesophagus, carries the risk of ulcer bleed after the band ligation, even more so in patients with ACLF owing to impaired coagulation function, occult infections and high portal pressure[146].

The management of acute variceal bleeding is similar in patients with ACLF as in patients with cirrhosis[12]. Pre-emptive trans-jugular intrahepatic portosystemic shunt (TIPS) placement has been shown to improve survival in patients with ACLF and acute variceal bleeding[147]. In general, the ideal patient for TIPS should have a MELD score of <17, but in patients with uncontrolled bleeding, a rescue TIPS can often be life-saving and can be considered up to a MELD score of 30 in patients with ACLF. However, among patients with ACLF who have liver failure, those with a high MELD score are at high risk of worsening of liver failure after TIPS placement, and an analysis on a case-by-case basis of the severity of bleed and the feasibility of salvage early liver transplantation is required[147].

Paracentesis is generally safe and is needed in one-third of patients with ACLF for management of ascites[87]. However, large-volume paracentesis is associated with a high risk of PICD in patients with ACLF as the ascites in these patients tends to be tense and inflammatory in nature, with high intra-abdominal pressure and high plasma renin activity (PRA)[12]. We investigated whether MVP (3 l to <5 l) could prevent development of PICD in patients with ACLF. However, PICD still developed in about 70% of patients with ACLF who underwent MVP. Co-administration of albumin reduced the incidence of PICD to 30% and was associated with reduced mortality[87]. A reduction in MAP of 5.3 mmHg on day 3 from baseline, and a PRA of 25 ng/ml per hour on day 3, was shown to predict development of PICD by day 6 (ref. 87). Midodrine is recommended before MVP in patients with ACLF as it increases MAP; the VITAL study showed that a combination of albumin and midodrine is superior to albumin alone in preventing development of PICD[143,148].

Specific therapies

Treatments for alcohol-associated ACLF. Patients with alcohol-associated ACLF present unique challenges owing to ongoing severe hepatitis with high bilirubin levels, impaired coagulation, co-existing infections, ascites and renal dysfunction (Supplementary Table 3). Corticosteroids showed limited efficacy in improving transplantation-free survival in the ACLF subgroup in the STOPAH trial, which investigated the efficacy of corticosteroids and pentoxifylline in patients with severe alcoholic hepatitis[149]. In a cohort of 1,249 patients from the AARC database, only 211 (16.9%) were eligible for steroid therapy. AARC ACLF grade III (score ≥10) was an independent predictor of steroid non-response[150]. To reduce the risk of infection while on steroids, granulocytopheresis (which removes granulocytes and monocytes from a patient's blood) and GCSF have shown benefit in patients with severe alcoholic hepatitis[151–153]. Combination therapy with prednisolone plus *N*-acetylcysteine increased 1-month survival in patients with severe acute alcoholic hepatitis but did not improve the primary outcome of 6-month survival[154].

Antiviral therapies for HBV-related ACLF. Nucleos(t)ide analogues should be started immediately in patients with HBV-related ACLF[1]. A study that investigated the efficacy of tenofovir in patients with HBV-related ACLF found that a greater than two-log reduction in HBV DNA levels at 2 weeks was an independent predictor of survival[155]. Patients with HBV-related ACLF and a MELD score of >30 should be prioritized for liver transplantation[1,2].

Corticosteroids for autoimmune hepatitis. Nearly 20% of patients with autoimmune hepatitis present with ACLF[156,157], and steroid therapy is helpful in selected patients. Patients with autoimmune

Box 1 | Preserving organ function in acute-on-chronic liver failure

Renal
- Avoid nephrotoxic antibiotics, antifungals and contrast agents

Cardiovascular
- Judicious use of fluids and albumin to prevent volume overload (use point-of-care ultrasonography to assess inferior vena cava distensibility, an indicator of volume status)
- Prevent mean arterial pressure <65 mmHg and >80 mmHg
- Use terlipressin to prevent after-load

Cerebral
- Use lactulose to avoid constipation and reduce absorption of ammonia

Coagulation
- Avoid unindicated correction of coagulopathy

Respiratory
- Avoid overload and pulmonary oedema
- Respiratory exercise to prevent atelectasis

Gastrointestinal
- Reduce intrabdominal pressure (<18 mmHg)
- Continue enteral or trophic feeding

Immune system and infection
- Measurement of biomarkers (C-reactive protein, procalcitonin and PCR-based viral and bacterial testing)
- Pre-emptive antimicrobial agents
- Early de-escalation of antimicrobial agents

hepatitis-related ACLF with a baseline MELD score od <27, without hepatic encephalopathy and with a fibrosis grade of <F3 might respond to steroid therapy with improved survival and reduced length of stay in the intensive care unit[158]. Dynamic severity score assessed while on therapy (a combination of an AARC score of >6, a MELD score of >2 and a SURFASA score of ≥−1.2 on day 3) might identify non-responders to steroid therapy[159]. The benefits and risks of corticosteroid treatment should ideally be assessed in each patient individually[157,160].

Reversal of ACLF syndrome. One of the main objectives of medical therapies for ACLF is to stabilize the patient and to attempt to preserve and regain the function of organs (Box 1) and, if possible, reverse the ACLF syndrome. As ACLF is an acute event, it can potentially be reversed once the acute insult is controlled. An analysis of the AARC database showed that 7.1% of ACLF survivors achieved a reversal of the syndrome (bilirubin <5 mg/dl, reversal of coagulopathy and no hepatic encephalopathy) by day 90 that was maintained for 1 year[161]. This study, which included 346 patients with ACLF, found a complete reversal of ACLF in 47% of patients within 3 months[161]. In another study, of 425 patients with HBV-related ACLF, 374 (88%) showed reversal of ACLF and in 90% of these stable reversal was maintained for up to 5 years[162]. In the CANONIC study, EASL–CLIF grade 1 ACLF resolved in 54.5% of patients and grade 3 ACLF resolved in 16% of patients[163], suggesting that the potential for reversibility may be inversely related to the ACLF severity. Reversal of ACLF should be attempted to provide patients an opportunity to survive with their native liver.

Liver transplantation in ACLF

Patient selection

Liver transplantation is life-saving in patients with severe ACLF. The decision to undertake liver transplantation depends on the recipient's clinical status, the availability of an organ or a living donor, and the potential for native liver recovery. The optimization of the patient in the interim period is essential and can help stabilize the majority of patients and reversal of ACLF in a small proportion of patients[12]. Urgent liver transplantation should be considered in patients with a MELD score of >30, AARC grade III, EASL–CLIF grade 3, or a COSSH score of 7–10 (refs. 2,14,164,165). Patients presenting with a MELD score of ≥40, AARC grade III with an AARC score of >13 and a CLIF-C ACLF score of ≥70 require evaluation by a multidisciplinary team owing to their higher risk of complications, potential for prolonged intensive care unit stay, increased resource utilization and poorer transplantation outcomes[99,166,167].

Time frame for liver transplantation

Patients with ACLF EASL–CLIF grade 3 or AARC grade III require urgent liver transplantation because of a high risk of mortality on waiting lists and delisting within the first 14 days as they deteriorate rapidly[168]. Efforts to actively manage and improve organ function in patients in order to downgrade ACLF from EASL–CLIF grade 3 to grade 1 or grade 2 has the potential to improve outcomes[12]. Delay in liver transplantation either owing to a lack of deceased donor organs or owing to logistical difficulties in living donor liver transplantation (LDLT) settings (for example, prolonged hospital stay, sepsis and organ failure). Early decision-making, especially in the LDLT setting, reduces financial burden on patients and health-care establishments[169]. Evidence suggests that as infections, sepsis and consequent organ failure develop within the first 7 days after the acute insult in patients with ACLF, patient selection for liver transplantation should be done in this 'golden window'[1,12,88,99]. In a study in 1,021 patients with ACLF from the AARC registry, 7-day mortality was 23.1% and 28-day mortality was 42.9%[99].

Contraindications for liver transplantation

Liver transplantation should not be considered in patients with ACLF who have any of the following conditions: uncontrolled, culture-positive bacterial infection or uncontrolled infection for >48 h; haemodynamic instability (noradrenaline dose exceeding 1 μg/kg/min); PaO_2/FiO_2 ratio <150; refractory gastrointestinal bleeding despite TIPS placement; CLIF-C ACLF score of >64 persisting for 3–7 days; failure of four or more organs; or serum lactate >90 mmol/l[99,167,170–172]. Patients in whom liver transplantation is not appropriate because of a high probability of mortality early after liver transplantation and an unacceptable quality of life should be referred for palliative care[173,174]. Unfortunately, in Asia, even with predominantly LDLT, <2.5% of patients with ACLF who were eligible for liver transplantation received liver transplantation[1,99]. In a multicentre study from Europe, the liver transplantation rate was low and varied from 0% to 29%, owing to the severity of illness (ACLF EASL–CLIF grade 3) in majority of the patients[175]. The rapid downhill disease course, lack of donors and lack of transplantation facilities were the main reasons for such a low rate of liver transplantation in patients with ACLF. The high mortality rates on waiting lists for patients with ACLF means that liver transplantation should be prioritized by giving

MELD exception points for AARC grade III ACLF (an allocation process in which parameters not included in MELD are considered)[79]. Undoubtedly, an urgent need exists for developing non-transplantation options for patients with ACLF.

Liver transplantation outcomes in ACLF

Liver transplantation outcomes in patients with ACLF have improved over time (Supplementary Table 4). In the ELITA/EF-CLIF collaborative study (ECLIS), which included 234 patients with ACLF, 1 year after liver transplantation survival was 81% in patients with grade 1ACLF, 72% in patients with grade 2 ACLF and 53% in patients with grade 3 ACLF[176]. Data from multicentre cohort studies and national registries showed approximately 80% survival at 1 year in patients with grade 3 ACLF selected for transplantation[177–179]. Many studies on liver transplantation in ACLF have focused on AARC cohorts and Asian populations. In one study involving 565 patients with ACLF who underwent liver transplantation, survival at 3 years was 76% in patients with AARC grade II ACLF and 61% in patients with AARC grade III ACLF[180]. Long-term post-transplantation mortality in patients with ACLF who undergo liver transplantation is primarily associated with biliary complications[181]. The reported results mostly come from patients with ACLF who received a good quality liver graft or in a LDLT setting with a graft-to-recipient-weight ratio close to 1 or a minimum graft weight of 650 g[182]. The expansion of the donor pool in LDLT to use grafts with a lower graft-to-recipient-weight ratio (0.65–0.80) with in-flow modulation, ABO-incompatible grafts, paired donor exchange (swap), and dual lobe grafts can mean that more patients receive transplants, but survival rates are lower[179], especially in those with multiorgan failure[182,183].

Experimental therapies

Artificial liver support systems and liver dialysis

Artificial liver support systems (ALSS) remove products of hepatocellular injury, such as DAMPs, toxic metabolites and cytokines (Supplementary Table 5), aiming to improve the haemodynamic and metabolic milieu; they can serve as a bridge to liver transplantation[184]. Despite theoretical benefits, most ALSS have demonstrated limited survival advantages in patients with ACLF[184]. DIALIVE, an extracorporeal liver dialysis device that aims to exchange dysfunctional albumin and remove DAMPs and PAMPs, shortened the recovery period in patients with alcohol-related ACLF but without survival benefits[185]. Among the

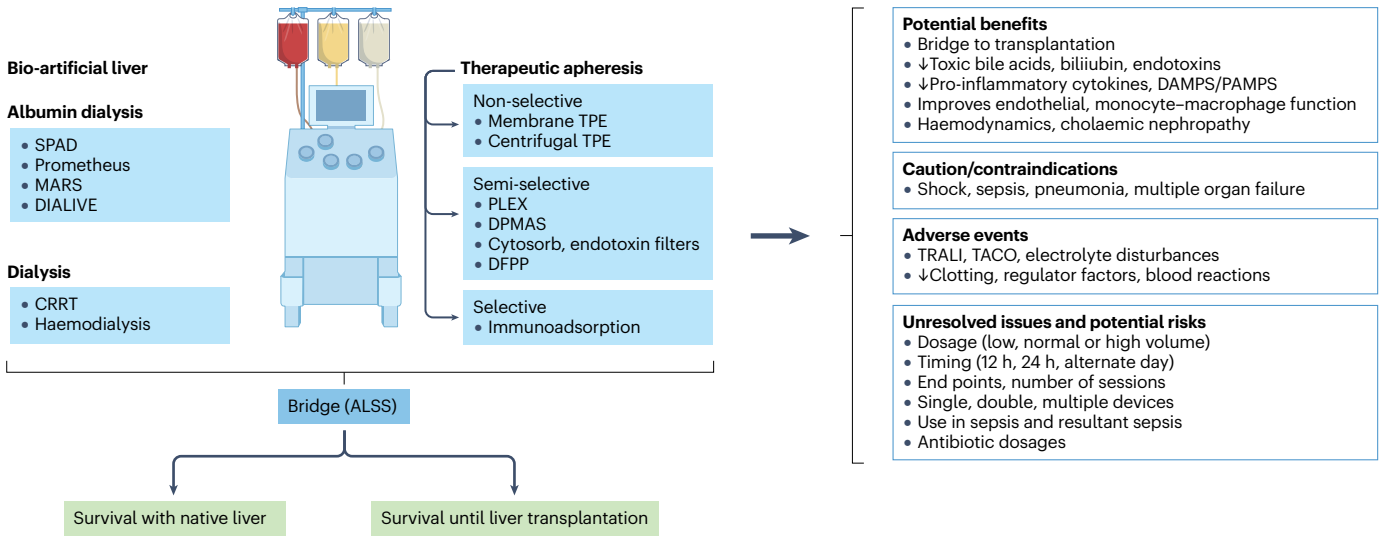
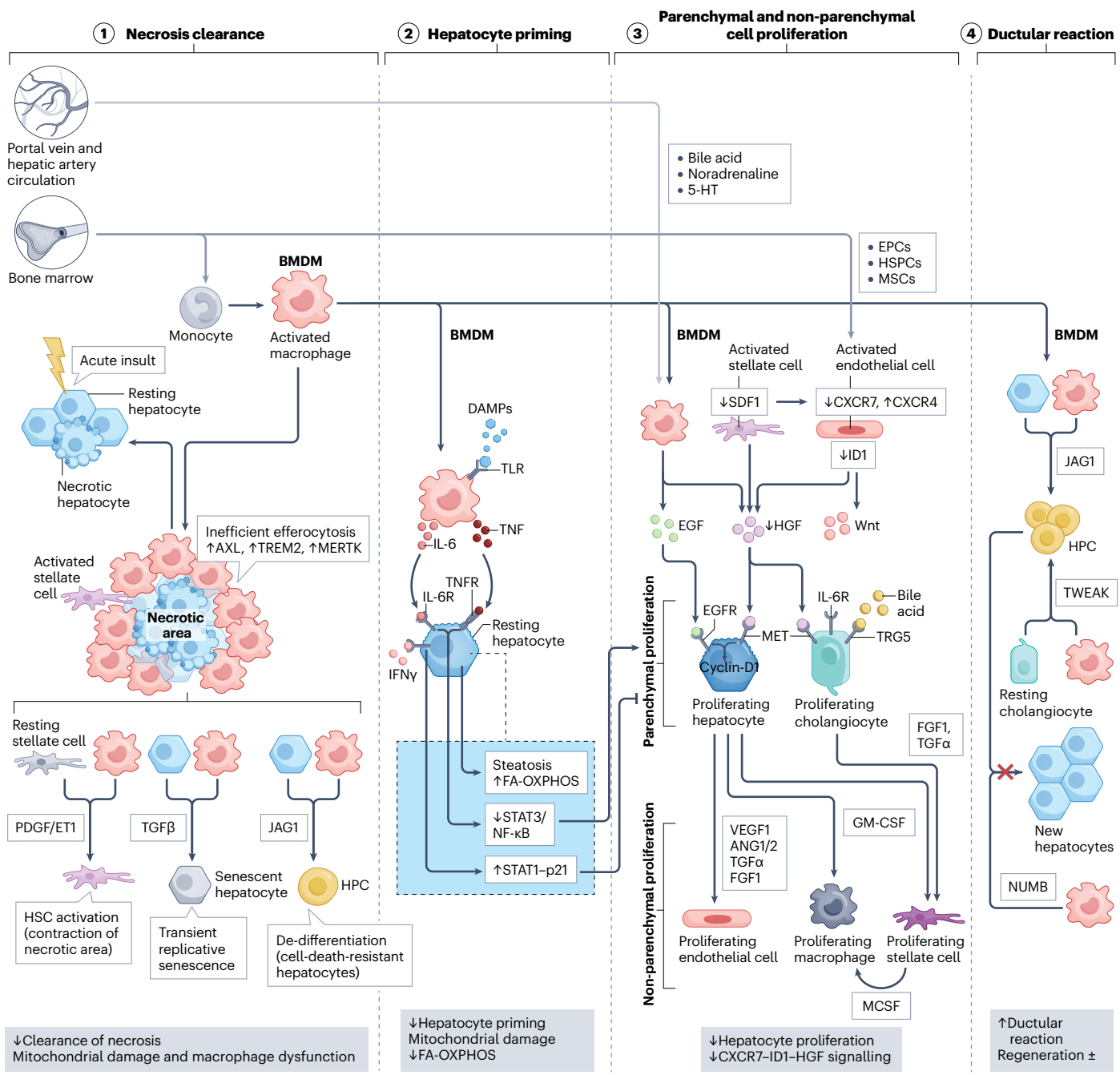


Fig. 5 | Artificial liver support in acute-on-chronic liver failure. Artificial liver support system (ALSS) often serves as a bridge to liver transplantation (for optimization of the function of organs in a patient while waiting for liver transplantation). ALSS can also serve as a bridge to recovery through augmentation of liver regeneration, removal of toxins and improvement in the inflammatory environment. ALSS can be categorized as either artificial or bio-artificial. Artificial ALSS such as single-pass albumin dialysis (SPAD), molecular adsorption recirculating system (MARS), Prometheus and the novel liver dialysis device DIALIVE use albumin-based techniques to bind and remove toxins from the blood. Therapeutic plasma exchange (TPE) and continuous renal replacement therapy (CRRT) are often considered albumin-independent, making them useful in specific cases. Bio-artificial ALSS incorporate hepatocytes within a bioreactor to support liver function. CRRT is more often used in acute liver failure than in acute-on-chronic liver failure (ACLF) with non-renal causes. In fact, it can lead to decreased clotting, haemodynamic instability and electrolyte disturbances. TPE can add to the risk of blood reactions, fluid overload and infections. Selective immunoadsorption, semi-selective double filtration plasmapheresis (DFPP) and non-selective TPE are used as experimental therapies in patients with ACLF. TPE is an emerging modality for patients with ACLF with membrane TPE being often favoured. In patients with ACLF, TPE should be initiated in the 'golden window' period during the first week after diagnosis to target sterile systemic inflammation, preventing multiple organ failure and infections. TPE can be delivered at different intensities — it can be given daily for three consecutive days or can be given intermittently and based on the patient's response. In patients with ACLF, an alternate-day strategy is often used with a maximum of eight sessions given with careful monitoring of laboratory values, clinical indicators, fluid overload, electrolyte disturbances and sepsis flares. Plasma exchange can be administered at high volume (10–15% of ideal body weight or 8–12 l or 2–3 × plasma volume), standard volume (5–6 l or 1.5–2 × plasma volume) or low volume (1.2 l or 0.5 × plasma volume). In patients with ACLF, TPE and ALSS can be futile and discontinuation should be considered in the following situations: non-response (Model for End-stage Liver Disease score >35, ACLF Research Consortium score >13, failure of four or more organs lasting for 4 days), haemodynamic instability, active uncontrolled sepsis, gastrointestinal bleeding and disseminated intravascular coagulation. DAMPs, damage-associated molecular patterns (DAMPs); DPMAS, double plasma molecular adsorption system; PAMPs, pathogen-associated molecular patterns; PLEX, plasma exchange; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury.



various modalities of ALSS, the double plasma molecular adsorption system utilizes two resins (one of which removes bile acids and bilirubin and the other that removes residual drugs, toxins and metabolic substances) and can reduce the incidence of new infections and organ failure in patients with ACLF[95] (Fig. 5).

Therapeutic plasma exchange

Therapeutic plasma exchange (TPE) reduces systemic inflammation, improves monocyte phagocytic function and improves mitochondrial respiration resulting in survival benefits compared with standard medical therapy in patients with ACLF[186]. A systematic review including 20 studies and 5,705 patients with ACLF found that TPE was associated with improved 30-day survival (RR 1.36; $P < 0.001$) and 90-day survival (RR 1.21; $P < 0.001$) over standard medical therapy; however, no differences in survival were seen when only randomized trials were analysed[187,188]. TPE, albumin dialysis and molecular adsorbent recirculating system are emerging therapies and can serve as a bridge to liver transplantation[185–187,189–193]. For TPE, the number of sessions and whether to use high-volume, standard-volume or low-volume TPE should be tailored to the individual patient.

Fig. 6 | Steps in liver regeneration and dysregulation of these steps in acute-on-chronic liver failure[1]. In necrosis clearance (1), damage-associated molecular patterns (DAMPs) produced by hepatocyte necrosis, necroptosis and proptosis lead to increased monocyte production and recruitment to the liver and their subsequent differentiation into bone-marrow-derived macrophages (BMDMs). Recruited BMDMs have a key role in the repair of necrotic liver lesions: they form a ring-like structure around the damaged area and limit the spread of necrosis (through inducing cell-death-resistant stem cell-like hepatocytes and hepatic stellate cell-mediated contraction of necrosis) and facilitate clearance of dying hepatocytes and immune cells by efferocytosis. In patients with acute-on-chronic liver failure (ACLF), necrosis clearance is markedly impaired owing to macrophage dysfunction[2]. Although monocyte production and recruitment is increased in patients with ACLF, the monocytes and macrophages show mitochondrial damage and bio-energy failure, which leads to functional exhaustion in both monocytes and liver BMDMs. In hepatocyte priming (2), following clearance of necrotic cells, IL-6 and TNF produced by macrophages induce the activation of signal transducer and activator of transcription 3 (STAT3), nuclear factor-κB (NF-κB) and YAP signalling in hepatocytes, which further leads to metabolic adaptation (transient steatosis and fatty acid-driven oxidative phosphorylation (FA-OXPHOS) and synthesis of various cell cycle proteins that prime the hepatocytes for proliferation. In patients with ACLF, this process is impaired owing to macrophage dysfunction, and a shift occurs from this pro-regenerative IL-6–STAT3 pathway to the anti-regenerative IFNγ–STAT1 pathway[210]. In parenchymal and non-parenchymal cell proliferation (3), growth factors such as epidermal growth factor (EGF), hepatocyte growth factor (HGF) and Wnt proteins produced by macrophages, stellate cells and endothelial cells drive the rapid proliferation of hepatocytes and cholangiocytes. Replicating hepatocytes and cholangiocytes produce growth factors that drive the subsequent proliferation of stellate cells, macrophages and endothelial cells. In patients with ACLF hepatocyte proliferation is markedly reduced owing to disruption of endothelial CXC-chemokine receptor 7 (CXCR7)–ID1–HGF signalling[209]. In ductular reaction (4), in situations where classic hepatocyte self-replication-mediated regeneration is impaired, the liver can still undergo a form of regeneration through an alternative pathway mediated by hepatic progenitor cells (HPCs) (a process known as a ductular reaction which involves HPCs proliferating and differentiating into both hepatocytes and cholangiocytes). In ACLF, the ductular reaction is greatly increased but is not always sufficient nor effective in promoting liver regeneration. 5-HT, 5-hydroxytryptamine; ANG, angiogenin; EGFR, epidermal growth factor receptor; EPC, endothelial progenitor cells; ET1, endothelin 1; GM-CSF, granulocyte–macrophage colony-stimulating factor; FGF1, fibroblast growth factor 1; HSCs, haematopoietic stem cells; HSPCs, haematopoietic stem and progenitor cells; MCSF, macrophage colony-stimulating factor; MSCs, mesenchymal stem cells; PDGF, platelet-derived growth factor; SDF1, stromal cell-derived factor 1; TGF, transforming growth factor; TLR, Toll-like receptor; TNFR, TNF receptor; VEGF1, vascular endothelial growth factor 1.

Therapies to modulate gut microbiota

Improving gut dysbiosis has shown potential in reducing morbidity and mortality among patients with ACLF[194–197]. In a pilot study in prednisolone-ineligible patients with severe alcoholic hepatitis, we observed that faecal microbiota transplantation (FMT) was associated with improved survival at day 90 compared with historical controls[198]. In a subsequent randomized trial of FMT administered through a nasoduodenal tube in patients with severe alcoholic hepatitis (57 of whom received prednisolone and 55 of whom received FMT), the 90-day survival was 75% in the FMT group versus 56.6% in the prednisolone group ($P = 0.04$)[40]. FMT resulted in reductions from baseline in pathogenic taxa (*Campylobacter*, Parcubacteria, *Weisella* and Leuconostocaceae), and an increase in beneficial taxa (Lachnospiraceae, *Prevotella* and *Veillonella*), indicating a major role of gut modulation in improving patient survival ($P < 0.05$)[40]. Although several patients in this trial had ACLF, the survival advantage with FMT needs to be validated in a large series of patients with ACLF. FMT has also been shown to decrease relapse of alcohol use disorder[199]. FMT as an adjunctive therapy to tenofovir was associated with improved transplant-free survival in patients with ACLF caused by HBV reactivation (and a MELD score of >18), compared with tenofovir alone[200].

Hepatic regeneration and related therapies in ACLF

Liver regeneration in response to parenchymal injury is a complex process that begins with BMDM-mediated clearance of necrotic tissue and inflammation[201,202]. Once the necrosis is cleared, BMDMs provide the growth factors for initiation and progression of hepatocyte proliferation[203–205] followed by proliferation of other parenchymal and non-parenchymal cells (Fig. 6). Compensatory hepatocyte proliferation in the face of aggressive liver injury is limited and inefficient in patients with ACLF[206–209], possibly owing to lack of supportive niche signals (CXCR7–ID1–hepatocyte growth factor (HGF) angiocrine signals) because of endothelial dysfunction[209] and a shift from pro-regenerative (IL-6–signal transducer and activator of transcription 3 (STAT3)) to anti-regenerative (IFNγ–STAT1) pathways because of defects in hepatic macrophage function[210]. Production of myeloid growth factors such as macrophage colony-stimulating factor and GCSF is also compromised in patients with ACLF, which leads to poor hepatocyte regeneration[209]. Bone marrow stem cell (BMSC) reserve is reduced in patients with cirrhosis[211,212], and in animal models this reduced BMSC reserve impeded hepatic regeneration[206]. Restoring monocyte energy using umbilical cord MSCs has been shown to ameliorate hepatic injury and promote liver regeneration in animal models of ACLF[50,56]. Our understanding of the hepatic and cholangiolar microenvironment and cellular metabolic milieu and the targets to stimulate hepatic regeneration in ACLF is limited.

Regenerative therapies in ACLF. Regenerative therapies in ACLF aim to modulate the hepatic microenvironment to promote regeneration of the remaining hepatic tissue. Both in vivo therapies (such as GCSF-mobilized BMSC therapy) and ex vivo cell-based therapies (such as MSC therapy) have shown promise.

GCSF therapy mobilizes haematopoietic stem cells from the bone marrow to the liver to support hepatocyte proliferation. In an RCT, GCSF was shown to reduce Child–Turcotte–Pugh score and improve short-term survival in patients with ACLF[213]. Subsequent studies and a meta-analysis of studies mostly conducted in Asian countries[214] showed that GCSF is associated with improvement in liver severity indices and survival in patients with ACLF (Supplementary Table 5). GCSF recruits dendritic cells to the liver and inhibits IFNγ-secreting $CD8^+$ T cells to ameliorate hepatocellular injury[215]. GCSF also improves neutrophil and macrophage functions[216,217]. GCSF therapy was not found to be superior to standard medical therapy in a study of European patients with ACLF, but >50% of these patients already had sepsis, AKI, hepatic encephalopathy and decompensated cirrhosis, and were possibly unsuitable for therapy[218]. Combining GCSF with a TLR4 inhibitor showed improved results (in terms of inhibition of inflammation, promotion of hepatic regeneration and prevention of mortality) over GCSF alone in animal models of ACLF[219]. Other growth factors and factors that mobilize

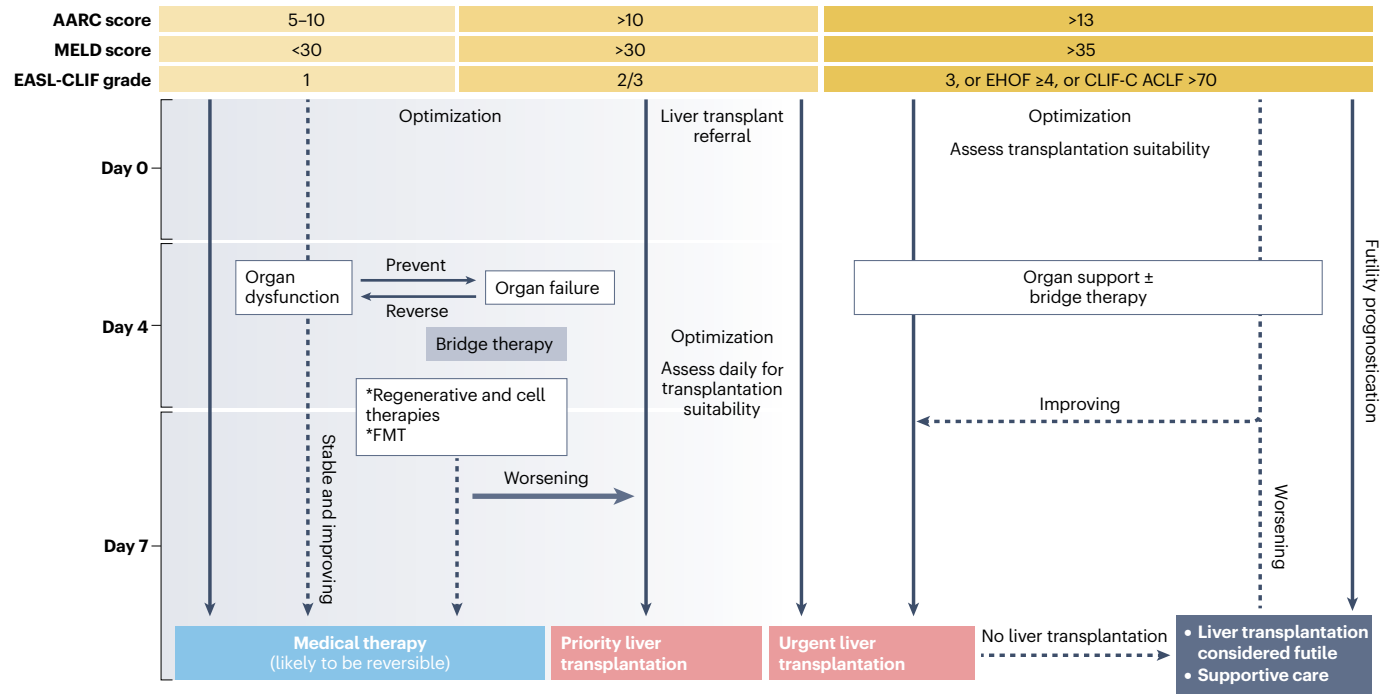


Fig. 7 | Suggested dynamic algorithm for the management of acute-on-chronic liver failure. Patients with acute-on-chronic liver failure (ACLF) often need a multidisciplinary approach, and this figure shows convergence of three scoring systems (ACLF Research Consortium (AARC) score, Model for End-stage Liver Disease (MELD) score, and the European Association for the Study of the Liver Chronic Liver Failure (EASL–CLIF) grade) in selected patients for medical therapy, priority transplantation, urgent transplantation or unsuitability for transplantation. Selection of patients to be shifted to intensive care is centre-specific, but we suggest a unified global approach subject to availability and affordability of resources. Managing nutrition, organ preservation, preventing infections and treating the acute insult are the cornerstones of managing a patient with ACLF. The treatment algorithm requires consideration of organ failure, disease severity score (using the AARC score, EASL–CLIF grade or the MELD score) in a dynamic manner on a daily basis. All patients should be evaluated for liver transplantation at admission to hospital. The severity of ACLF and the patient's response to treatment can fluctuate daily, making it difficult to predict the best course of action and necessitating frequent and comprehensive assessments to tailor bridging therapies and determine transplant suitability. Regenerative therapies, cell-based therapies and faecal microbiota transplantation (FMT) are still considered experimental and under research, and should be used selectively under clinical protocols. Decisions around futility of care, futility of liver transplantation and shifting to hospice care or end-of-life support are centre-specific. Priority for liver transplantation should be determined in the first or second week after diagnosis in patients with ACLF, and patients presenting with EASL–CLIF grade 3 or progressing from grade 2 to 3 ACLF who need urgent liver transplantation should be considered in the first week. Survival with native liver should always be attempted and is dependent on timely, specific therapies for the underlying insult, continuous assessment, especially on day 4, a critical time point for assessing response to treatment during the first 72 h and making decisions about ongoing management and consideration of other therapies. Liver transplantation can be offered to a very small fraction globally (<5% of patients with ACLF receive an organ for liver transplantation[19,99,175]). asterisks, experimental therapy; EHOF, extrahepatic organ failure. Adapted from ref. 12, Springer Nature Limited.

bone marrow cells such as augmenter of liver regeneration, hepatocyte growth factor, vascular endothelial growth factor and bone marrow cell-mobilizing factors (for example, plerixafor) are under evaluation for liver regeneration in patients with decompensated cirrhosis[220,221].

MSCs possess regenerative and immunomodulatory capabilities and have been used as therapeutic agents in patients with ACLF (Supplementary Table 4). A pivotal clinical trial involving 110 patients with HBV-associated ACLF demonstrated that MSC therapy is safe, reduces liver injury and improves 24-week survival, especially in the early or plateau phase of ACLF[222]. The plasma microenvironment in ACLF can affect the function of MSCs[223,224], and TPE can enhance MSC efficacy[225,226]. Extracellular vesicles released by MSCs have a pivotal role in their therapeutic effect. Preclinical studies in ACLF have shown that extracellular vesicles modulate autophagy, reduce hepatic injury and improve liver function[227,228]. Further studies are required to optimize treatment protocols, cell source, dosage, administration route, and timing of cell-based therapy for patients with ACLF.

Conclusions

Managing a patient with ACLF depends on the patient population, regional health practices and available medical expertise. Patients with ACLF who present to the outpatient department can be managed by internists, gastroenterologists and hepatologists, while those presenting to the emergency department should be managed by hepatologists, intensivists and infectious disease specialists in collaboration with the liver transplant team. Management of the patient should aim to preserve the function and reverse the failure of organs, prevent and manage infections, and mitigate the acute insult to enable the liver to regenerate and achieve functional viability. An algorithmic approach to managing patients with different severities of ACLF (Fig. 7)

is helpful and can be modified on a dynamic basis to assess management by the medical team, and the urgency or futility of liver transplantation.

In conclusion, ACLF is a distinct and severe syndrome that requires rapid diagnosis and tailored management given its high short-term mortality. Seminal advances in elucidating the pathophysiology of ACLF have highlighted that hepatocellular injury is a key driver of systemic inflammation and that immune dysregulation, organ dysfunction and organ failure are associated with poor outcomes. Although liver transplantation remains the cornerstone of definitive management, it is often not feasible. Some emerging novel therapies that target immune modulation, provide organ support, and modify the gut microbiota are promising. The recent 'Kyoto ACLF Consensus' — which provides a strong basis for standardizing ACLF definitions, describing dysfunction and failure of organs, and refining prognostic tools and management protocols — will hopefully help to improve patient outcomes.

Published online: 05 January 2026

References

1. Sarin, S. K. et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL): an update. *Hepatol. Int.* **13**, 353–390 (2019).
2. Sarin, S. K. & Choudhury, A. Acute-on-chronic liver failure: terminology, mechanisms and management. *Nat. Rev. Gastroenterol. Hepatol.* **13**, 131–149 (2016).
3. Imura, S., Shimada, M. & Utsunomiya, T. Recent advances in estimating hepatic functional reserve in patients with chronic liver damage. *Hepatol. Res.* **45**, 10–19 (2015).
4. Chapelle, T. et al. Future remnant liver function estimated by combining liver volumetry on magnetic resonance imaging with total liver function on ^{99m}Tc-mebrofenin hepatobiliary scintigraphy: can this tool predict post-hepatectomy liver failure? *HPB* **18**, 494–503 (2016).
5. Previs, S. F. et al. Quantifying rates of protein synthesis in humans by use of $^{2}H_{2}O$: application to patients with end-stage renal disease. *Am. J. Physiol. Endocrinol. Metab.* **286**, E665–E672 (2004).
6. European Association for the Study of the Liver EASL clinical practice guidelines on acute-on-chronic liver failure. *J. Hepatol.* **79**, 461–491 (2023).
7. Moreau, R. et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* **144**, 1426–1437.e9 (2013).
8. Torre, A. et al. Consensus document on acute-on-chronic liver failure (ACLF) established by the Mexican Association of Hepatology. *Ann. Hepatol.* **28**, 101140 (2023).
9. Nakayama, N. et al. Nationwide survey for patients with acute-on-chronic liver failure occurring between 2017 and 2019 and diagnosed according to proposed Japanese criteria. *J. Gastroenterol.* **56**, 1092–1106 (2021).
10. Kulkarni, A. V. & Sarin, S. K. Acute-on-chronic liver failure — steps towards harmonization of the definition!. *J. Hepatol.* **81**, 360–366 (2024).
11. Trebicka, J. et al. PREDICT identifies precipitating events associated with the clinical course of acutely decompensated cirrhosis. *J. Hepatol.* **74**, 1097–1108 (2021).
12. Choudhury, A. et al. Acute-on-chronic liver failure (ACLF): the 'Kyoto Consensus' — steps from Asia. *Hepatol. Int.* **19**, 1–69 (2025).
13. Choudhury, A., Adali, G., Kaewdech, A., Giri, S. & Kumar, R. Liver transplantation in chronic liver disease and acute on chronic liver failure — indication, timing and practices. *J. Clin. Exp. Hepatol.* **14**, 101347 (2024).
14. Artru, F., Trovato, F., Morrison, M., Bernal, W. & McPhail, M. Liver transplantation for acute-on-chronic liver failure. *Lancet Gastroenterol. Hepatol.* **9**, 564–576 (2024).
15. Jalan, R. et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. *J. Hepatol.* **61**, 1038–1047 (2014).
16. Farias, A. Q. et al. Genetic ancestry, race, and severity of acutely decompensated cirrhosis in Latin America. *Gastroenterology* **165**, 696–716 (2023).
17. Mochida, S. et al. Diagnostic criteria for acute-on-chronic liver failure and related disease conditions in Japan. *Hepatol. Res.* **52**, 417–421 (2022).
18. Kumar, A. et al. Impact of diabetes, drug-induced liver injury, and sepsis on outcomes in metabolic dysfunction associated fatty liver disease-related acute-on-chronic liver failure. *Am. J. Gastroenterol.* **120**, 816–826 (2025).
19. Bajaj, J. S. et al. Global disparities in mortality and liver transplantation in hospitalised patients with cirrhosis: a prospective cohort study for the CLEARED Consortium. *Lancet Gastroenterol. Hepatol.* **8**, 611–622 (2023).
20. Devarbhavi, H. et al. Drug-induced liver injury: Asia Pacific Association of Study of Liver consensus guidelines. *Hepatol. Int.* **15**, 258–282 (2021).
21. Gerussi, A. et al. Immune-mediated drug-induced liver injury: immunogenetics and experimental models. *Int. J. Mol. Sci.* **22**, 4557 (2021).
22. Fontana, R. J. et al. AASLD practice guidance on drug, herbal, and dietary supplement-induced liver injury. *Hepatology* **77**, 1036–1065 (2023).
23. Kulkarni, A. V. et al. *Tinospora cordifolia* (Giloy)-induced liver injury during the COVID-19 pandemic-multicenter nationwide study from India. *Hepatol. Commun.* **6**, 1289–1300 (2022).
24. Shen, T. et al. Incidence and etiology of drug-induced liver injury in mainland China. *Gastroenterology* **156**, 2230–2241.e11 (2019).
25. Devarbhavi, H. et al. Drug-induced acute-on-chronic liver failure in Asian patients. *Am. J. Gastroenterol.* **114**, 929–937 (2019).
26. Albillos, A. et al. Cirrhosis-associated immune dysfunction. *Nat. Rev. Gastroenterol. Hepatol.* **19**, 112–134 (2022).
27. Clària, J. et al. Systemic inflammation in decompensated cirrhosis: characterization and role in acute-on-chronic liver failure. *Hepatology* **64**, 1249–1264 (2016).
28. Macdonald, S. et al. Cell death markers in patients with cirrhosis and acute decompensation. *Hepatology* **67**, 989–1002 (2018).
29. Khanam, A. et al. Blockade of neutrophil's chemokine receptors CXCR1/2 abrogate liver damage in acute-on-chronic liver failure. *Front. Immunol.* **8**, 464 (2017).
30. Szabo, G. & Petrasek, J. Inflammasome activation and function in liver disease. *Nat. Rev. Gastroenterol. Hepatol.* **12**, 387–400 (2015).
31. Singh, S. P. et al. Bowel colonization with carbapenem-resistant bacteria is associated with short-term outcomes in patients with acute-on-chronic liver failure. *J. Gastroenterol. Hepatol.* **40**, 528–536 (2025).
32. Medzhitov, R. Origin and physiological roles of inflammation. *Nature* **454**, 428–435 (2008).
33. Artru, F. & McPhail, M. J. Immunopathogenesis of acute on chronic liver failure. *Am. J. Transpl.* **24**, 724–732 (2024).
34. Alcaraz-Quiles, J. et al. Polymorphisms in the IL-1 gene cluster influence systemic inflammation in patients at risk for acute-on-chronic liver failure. *Hepatology* **65**, 202–216 (2017).
35. Monteiro, S. et al. Differential inflammasome activation predisposes to acute-on-chronic liver failure in human and experimental cirrhosis with and without previous decompensation. *Gut* **70**, 379–387 (2021).
36. Kuwabara, S., Goggins, E. & Okusa, M. D. The pathophysiology of sepsis-associated AKI. *Clin. J. Am. Soc. Nephrol.* **17**, 1050–1069 (2022).
37. Nadim, M. K. & Garcia-Tsao, G. Acute kidney injury in patients with cirrhosis. *N. Engl. J. Med.* **388**, 733–745 (2023).
38. Liu, T., Zhang, L., Joo, D. & Sun, S. C. NF-κB signaling in inflammation. *Signal. Transduct. Target. Ther.* **2**, 17023 (2017).
39. Solé, C. et al. Alterations in gut microbiome in cirrhosis as assessed by quantitative metagenomics: relationship with acute-on-chronic liver failure and prognosis. *Gastroenterology* **160**, 206–218.e13 (2021).
40. Pande, A. et al. Fecal microbiota transplantation compared with prednisolone in severe alcoholic hepatitis patients: a randomized trial. *Hepatol. Int.* **17**, 249–261 (2023).
41. Bao, Z. et al. Landscapes of gut microbiome and bile acid signatures and their interaction in HBV-associated acute-on-chronic liver failure. *Front. Microbiol.* **14**, 1185993 (2023).
42. Sparfel, L., Ratodiarivony, S., Boutet-Robinet, E., Ellero-Simatos, S. & Jolivet-Gougeon, A. *Akkermansia muciniphila* and alcohol-related liver diseases. a systematic review. *Mol. Nutr. Food Res.* **68**, e2300510 (2024).
43. Lang, S. et al. Intestinal fungal dysbiosis and systemic immune response to fungi in patients with alcoholic hepatitis. *Hepatology* **71**, 522–538 (2020).
44. Zeng, Y., Gan, D., Zeng, Y. & Xiong, M. Exploring the interaction between bile acid and intestinal microbiota in acute-onchronic liver failure and the progress of treatment strategies. *J. Gastroenterol. Res. Pract.* **4**, 1195 (2024).
45. Martins, R. et al. Disease tolerance as an inherent component of immunity. *Annu. Rev. Immunol.* **37**, 405–437 (2019).
46. Moreau, R. et al. Blood metabolomics uncovers inflammation-associated mitochondrial dysfunction as a potential mechanism underlying ACLF. *J. Hepatol.* **72**, 688–701 (2020).
47. McPhail, M. J. W. et al. Multivariate metabotyping of plasma predicts survival in patients with decompensated cirrhosis. *J. Hepatol.* **64**, 1058–1067 (2016).
48. Clària, J., Arroyo, V. & Moreau, R. Roles of systemic inflammatory and metabolic responses in the pathophysiology of acute-on-chronic liver failure. *JHEP Rep.* **5**, 100807 (2023).
49. Engelmann, C., Zhang, I. W. & Clària, J. Mechanisms of immunity in acutely decompensated cirrhosis and acute-on-chronic liver failure. *Liver Int.* **45**, e15644 (2025).
50. Maheshwari, D. et al. Bioenergetic failure drives functional exhaustion of monocytes in acute-on-chronic liver failure. *Front. Immunol.* **13**, 856587 (2022).
51. Korf, H. et al. Inhibition of glutamine synthetase in monocytes from patients with acute-on-chronic liver failure resuscitates their antibacterial and inflammatory capacity. *Gut* **68**, 1872–1883 (2019).
52. Li, J. et al. PBMC transcriptomics identifies immune-metabolism disorder during the development of HBV-ACLF. *Gut* **71**, 163–175 (2022).
53. Yuan, W. et al. High expression of interleukin-33/ST2 predicts the progression and poor prognosis in chronic hepatitis B patients with hepatic flare. *Am. J. Med. Sci.* **360**, 656–661 (2020).
54. Venet, F. & Monneret, G. Advances in the understanding and treatment of sepsis-induced immunosuppression. *Nat. Rev. Nephrol.* **14**, 121–137 (2018).
55. Cheng, S. C. et al. Broad defects in the energy metabolism of leukocytes underlie immunoparalysis in sepsis. *Nat. Immunol.* **17**, 406–413 (2016).
56. Li, W., Yang, Y., Yang, L., Chang, N. & Li, L. Monocyte-derived Kupffer cells dominate in the Kupffer cell pool during liver injury. *Cell Rep.* **42**, 113164 (2023).

57. Sehgal, R. et al. Granulocyte-macrophage colony-stimulating factor modulates myeloid-derived suppressor cells and Treg activity in decompensated cirrhotic patients with sepsis. *Front. Immunol.* **13**, 828949 (2022).
58. Yadav, P. et al. Soluble factors and suppressive monocytes can predict early development of sepsis in acute-on-chronic liver failure. *Hepatol. Commun.* **6**, 2105–2120 (2022).
59. Baweja, S. et al. Circulating extracellular vesicles induce monocyte dysfunction and are associated with sepsis and high mortality in cirrhosis. *Liver Int.* **41**, 1614–1628 (2021).
60. Sukriti, S. et al. Microvesicles in hepatic and peripheral vein can predict nonresponse to corticosteroid therapy in severe alcoholic hepatitis. *Aliment. Pharmacol. Ther.* **47**, 1151–1161 (2018).
61. Bukong, T. N. et al. Abnormal neutrophil traps and impaired efferocytosis contribute to liver injury and sepsis severity after binge alcohol use. *J. Hepatol.* **69**, 1145–1154 (2018).
62. Bernsmeier, C. et al. Patients with acute-on-chronic liver failure have increased numbers of regulatory immune cells expressing the receptor tyrosine kinase MERTK. *Gastroenterology* **148**, 603–615.e14 (2015).
63. Sharma, N. et al. Plasma lipidomics and fungal peptide-based community analysis identifies distinct signatures of early mortality in acute liver failure. *Clin. Mol. Hepatol.* **31**, 1233–1251 (2025).
64. Feio-Azevedo, R. et al. Distinct immunometabolic signatures in circulating immune cells define disease outcome in acute-on-chronic liver failure. *Hepatology* **81**, 509–522 (2025).
65. Bernsmeier, C. et al. Leucocyte ratios are biomarkers of mortality in patients with acute decompensation of cirrhosis and acute-on-chronic liver failure. *Aliment. Pharmacol. Ther.* **52**, 855–865 (2020).
66. Wu, W. et al. Circulating neutrophil dysfunction in HBV-related acute-on-chronic liver failure. *Front. Immunol.* **12**, 620365 (2021).
67. Zhao, Q. et al. NK-cell-elicited gasdermin-D-dependent hepatocyte pyroptosis induces neutrophil extracellular traps that facilitate HBV-related acute-on-chronic liver failure. *Hepatology* **81**, 917–931 (2025).
68. Li, X. et al. FGL2-MCOLN3-autophagy axis-triggered neutrophil extracellular traps exacerbate liver injury in fulminant viral hepatitis. *Cell Mol. Gastroenterol. Hepatol.* **14**, 1077–1101 (2022).
69. Yadav, M. et al. Circulating urobilinogen augments inflammation and corticosteroid non-response in severe alcohol-induced hepatitis. *Mol. Ther.* **33**, 5263–5280 (2025).
70. Cho, Y. et al. Neutrophil extracellular traps contribute to liver damage and increase defective low-density neutrophils in alcohol-associated hepatitis. *J. Hepatol.* **78**, 28–44 (2023).
71. Boussif, A. et al. Impaired intracellular signaling, myeloperoxidase release and bactericidal activity of neutrophils from patients with alcoholic cirrhosis. *J. Hepatol.* **64**, 1041–1048 (2016).
72. Garg, V. et al. Granulocyte colony-stimulating factor mobilizes $CD34^+$ cells and improves survival of patients with acute-on-chronic liver failure. *Gastroenterology* **142**, 505–512.e1 (2012).
73. Rueschenbaum, S. et al. Dysregulated adaptive immunity is an early event in liver cirrhosis preceding acute-on-chronic liver failure. *Front. Immunol.* **11**, 534731 (2020).
74. Yu, X. et al. BTLA contributes to acute-on-chronic liver failure infection and mortality through $CD4^+$ T-cell exhaustion. *Nat. Commun.* **15**, 1835 (2024).
75. Zhao, Y. et al. Characterization of intrahepatic B cells in acute-on-chronic liver failure. *Front. Immunol.* **13**, 1041176 (2022).
76. Das, S. et al. Hyperoxidized albumin modulates neutrophils to induce oxidative stress and inflammation in severe alcoholic hepatitis. *Hepatology* **65**, 631–646 (2017).
77. Jagdish, R. K., Maras, J. S. & Sarin, S. K. Albumin in advanced liver diseases: the good and bad of a drug!. *Hepatology* **74**, 2848–2862 (2021).
78. Carvalho, J. R. & Verdelho Machado, M. New insights about albumin and liver disease. *Ann. Hepatol.* **17**, 547–560 (2018).
79. Sarin, S. K. & Choudhury, A. Management of acute-on-chronic liver failure: an algorithmic approach. *Hepatol. Int.* **12**, 402–416 (2018).
80. Sarin, S. K. & Choudhury, A. Acute-on-chronic liver failure. *Curr. Gastroenterol. Rep.* **18**, 61 (2016).
81. Jindal, A. et al. Severity of acute portal hypertension determines the clinical outcomes in severe alcoholic hepatitis. *Dig. Dis. Sci.* **69**, 298–307 (2024).
82. Garg, H. et al. Hepatic and systemic hemodynamic derangements predict early mortality and recovery in patients with acute-on-chronic liver failure. *J. Gastroenterol. Hepatol.* **28**, 1361–1367 (2013).
83. Kumar, A. et al. Hemodynamic studies in acute-on-chronic liver failure. *Dig. Dis. Sci.* **54**, 869–878 (2009).
84. Kumar, M. et al. Treatment with carvedilol improves survival of patients with acute-on-chronic liver failure: a randomized controlled trial. *Hepatol. Int.* **13**, 800–813 (2019).
85. Sharma et al. Acute variceal bleeding portends poor outcomes in patients with acute-on-chronic liver failure: a propensity score matched study from the APASL ACLF Research Consortium (AARC). *Hepatol. Int.* **16**, 1234–1243 (2022).
86. Mutlu, U. et al. Intra-abdominal hypertension and its prognostic impact on mortality in cirrhotic patients with ascites: the role of paracentesis. *Turk. J. Gastroenterol.* **36**, 390–397 (2025).
87. Arora, V. et al. Paracentesis-induced circulatory dysfunction with modest-volume paracentesis is partly ameliorated by albumin infusion in acute-on-chronic liver failure. *Hepatology* **72**, 1043–1055 (2020).
88. Choudhury, A. et al. Systemic inflammatory response syndrome in acute-on-chronic liver failure: relevance of 'golden window': a prospective study. *J. Gastroenterol. Hepatol.* **32**, 1989–1997 (2017).
89. Mahmud, N. et al. The predictive role of model for end-stage liver disease — lactate and lactate clearance for in-hospital mortality among a national cirrhosis cohort. *Liver Transpl.* **27**, 177–189 (2021).
90. Sarmast, N. et al. Model for end-stage liver disease — lactate and prediction of inpatient mortality in patients with chronic liver disease. *Hepatology* **72**, 1747–1757 (2020).
91. Li, J. et al. Development and validation of a new prognostic score for hepatitis B virus-related acute-on-chronic liver failure. *J. Hepatol.* **75**, 1104–1115 (2021).
92. Bajaj, J. S. et al. Defining organ failures in patients with cirrhosis: consensus statements. *Gastroenterology* **169**, 1043–1062 (2025).
93. Luo, J. et al. Predicting the onset of hepatitis B virus-related acute-on-chronic liver failure. *Clin. Gastroenterol. Hepatol.* **21**, 681–693 (2023).
94. Zhang, Y. et al. Metabolic biomarkers significantly enhance the prediction of HBV-related ACLF occurrence and outcomes. *J. Hepatol.* **79**, 1159–1171 (2023).
95. Yadav, M. et al. Comparative metabolome analysis reveals higher potential of haemoperfusion adsorption in providing favourable outcome in ACLF patients. *Liver Int.* **44**, 1189–1201 (2024).
96. Maras, J. S. et al. Dysregulated iron homeostasis is strongly associated with multiorgan failure and early mortality in acute-on-chronic liver failure. *Hepatology* **61**, 1306–1320 (2015).
97. Luo, J. et al. Acute-on-chronic liver failure: far to go — a review. *Crit. Care* **27**, 259 (2023).
98. Li, P., Liang, X., Luo, J. & Li, J. Omics in acute-on-chronic liver failure. *Liver Int.* **45**, e15634 (2025).
99. Choudhury, A. et al. 'First week' is the crucial period for deciding living donor liver transplantation in patients with acute-on-chronic liver failure. *Hepatol. Int.* **15**, 1376–1388 (2021).
100. Cao, Z. et al. Global prevalence and characteristics of infections and clinical outcomes in hospitalised patients with cirrhosis: a prospective cohort study for the CLEARED Consortium. *Lancet Gastroenterol. Hepatol.* **9**, 997–1009 (2024).
101. Chen, T. et al. Expert consensus on the diagnosis and treatment of end-stage liver disease complicated by infections. *Hepatol. Int.* **18**, 817–832 (2024).
102. Li, B. et al. Prognostic and therapeutic significance of microbial cell-free DNA in plasma of people with acute decompensation of cirrhosis. *J. Hepatol.* **78**, 322–332 (2023).
103. Shi, P. et al. Application of metagenomic next-generation sequencing in optimizing the diagnosis of ascitic infection in patients with liver cirrhosis. *BMC Infect. Dis.* **24**, 503 (2024).
104. Wu, H. X. et al. Clinical evaluation of metagenomic next-generation sequencing method for the diagnosis of suspected ascitic infection in patients with liver cirrhosis in a clinical laboratory. *Microbiol. Spectr.* **11**, e0294622 (2023).
105. Jiang, Y. et al. Clinical characteristics and early diagnosis of spontaneous fungal peritonitis/fungiascites in hospitalized cirrhotic patients with ascites: a case-control study. *J. Clin. Med.* **12**, 3100 (2023).
106. Maiwall, R. et al. APASL clinical practice guidelines on the management of acute kidney injury in acute-on-chronic liver failure. *Hepatol. Int.* **18**, 833–869 (2024).
107. O'Leary, J. G. et al. NACSELD acute-on-chronic liver failure (NACSELD-ACLF) score predicts 30-day survival in hospitalized patients with cirrhosis. *Hepatology* **67**, 2367–2374 (2018).
108. Maiwall, R. et al. AKI in patients with acute on chronic liver failure is different from acute decompensation of cirrhosis. *Hepatol. Int.* **9**, 627–639 (2015).
109. Arora, V. et al. Terlipressin is superior to noradrenaline in the management of acute kidney injury in acute on chronic liver failure. *Hepatology* **71**, 600–610 (2020).
110. Belcher, J. M. et al. Terlipressin and the treatment of hepatorenal syndrome: how the CONFIRM trial moves the story forward. *Am. J. Kidney Dis.* **79**, 737–745 (2022).
111. Jindal, A. et al. Early versus standard initiation of terlipressin for acute kidney injury in ACLF: a randomized controlled trial (eTerli Study). *Dig. Dis. Sci.* **69**, 2204–2214 (2024).
112. Badal, B. D. & Bajaj, J. S. Hepatic encephalopathy in acute-on-chronic liver failure. *Clin. Liver Dis.* **27**, 691–702 (2023).
113. Verma, N. et al. Dynamic assessments of hepatic encephalopathy and ammonia levels predict mortality in acute-on-chronic liver failure. *Hepatol. Int.* **15**, 970–982 (2021).
114. Wright, G., Sharifi, Y., Jover-Cobos, M. & Jalan, R. The brain in acute on chronic liver failure. *Metab. Brain Dis.* **29**, 965–973 (2014).
115. Maiwall, R. & Sarin, S. K. Plasma exchange in acute and acute on chronic liver failure. *Semin. Liver Dis.* **41**, 476–494 (2021).
116. Tan, E. X., Wang, M. X., Pang, J. & Lee, G. H. Plasma exchange in patients with acute and acute-on-chronic liver failure: a systematic review. *World J. Gastroenterol.* **26**, 219–245 (2020).
117. Tripodi, A., Caldwell, S. H., Hoffman, M., Trotter, J. F. & Sanyal, A. J. Review article: the prothrombin time test as a measure of bleeding risk and prognosis in liver disease. *Aliment. Pharmacol. Ther.* **26**, 141–148 (2007).
118. Premkumar, M. & Sarin, S. K. Current concepts in coagulation profile in cirrhosis and acute-on-chronic liver failure. *Clin. Liver Dis.* **16**, 158–167 (2020).
119. Premkumar, M. et al. Coagulation failure is associated with bleeding events and clinical outcome during systemic inflammatory response and sepsis in acute-on-chronic liver failure: an observational cohort study. *Liver Int.* **39**, 694–704 (2019).
120. Blasi, A. et al. Coagulation failure in patients with acute-on-chronic liver failure and decompensated cirrhosis: beyond the international normalized ratio. *Hepatology* **68**, 2325–2337 (2018).
121. Ma, J., Björnsson, E. S. & Chalasani, N. Hepatotoxicity of antibiotics and antifungals and their safe use in hepatic impairment. *Semin. Liver Dis.* **44**, 239–257 (2024).

122. O'Leary, J. G., Greenberg, C. S., Patton, H. M. & Caldwell, S. H. AGA clinical practice update: coagulation in cirrhosis. *Gastroenterology* **157**, 34–43.e1 (2019).
123. Schulz, M. S. et al. Pulmonary impairment independently determines mortality in critically ill patients with acute-on-chronic liver failure. *Liver Int.* **43**, 180–193 (2023).
124. Nanchal, R. et al. Guidelines for the management of adult acute and acute-on-chronic liver failure in the ICU: cardiovascular, endocrine, hematologic, pulmonary, and renal considerations. *Crit. Care Med.* **48**, e173–e191 (2020).
125. Berger, M. M. & Hurni, C. A. Management of gastrointestinal failure in the adult critical care setting. *Curr. Opin. Crit. Care* **28**, 190–197 (2022).
126. Oami, T. et al. Gut integrity in intensive care: alterations in host permeability and the microbiome as potential therapeutic targets. *J. Intensive Care* **13**, 16 (2025).
127. Soranno, D. E. et al. A review of gut failure as a cause and consequence of critical illness. *Crit. Care* **29**, 91 (2025).
128. Vijayaraghavan, R. et al. Reversal of feed intolerance by prokinetics improves survival in critically Ill cirrhosis patients. *Dig. Dis. Sci.* **67**, 4223–4233 (2022).
129. Liu, J. J., Venkatesh, V., Gao, J., Adler, E. & Brenner, D. M. Efficacy and safety of neostigmine and decompressive colonoscopy for acute colonic pseudo-obstruction: a single-center analysis. *Gastroenterol. Res.* **14**, 157–164 (2021).
130. Tripathi, H. et al. Identifying critically ill patients with cirrhosis who benefit from nutrition therapy: the mNUTRIC score study. *J. Clin. Transl. Res.* **8**, 425–433 (2022).
131. Plauth, M. et al. ESPEN guideline on clinical nutrition in liver disease. *Clin. Nutr.* **38**, 485–521 (2019).
132. Geng, N. et al. Association of myosteatosis with short-term outcomes in patients with acute-on-chronic liver failure. *Sci. Rep.* **14**, 13609 (2024).
133. Kulkarni, A. V. et al. Omega-3 fatty acid lipid emulsions are safe and effective in reducing endotoxemia and sepsis in acute-on-chronic liver failure: an open-label randomized controlled trial. *J. Gastroenterol. Hepatol.* **36**, 1953–1961 (2021).
134. Hou, W. et al. Effect of a carbohydrate-containing late-evening snack on energy metabolism and fasting substrate utilization in adults with acute-on-chronic liver failure due to hepatitis B. *Eur. J. Clin. Nutr.* **67**, 1251–1256 (2013).
135. Incicco, S., Angeli, P. & Piano, S. Bacterial infections in acute on chronic liver failure. *Clin. Liver Dis.* **27**, 703–716 (2023).
136. Philips, C. A. et al. Comparison of 5% human albumin and normal saline for fluid resuscitation in sepsis induced hypotension among patients with cirrhosis (FRISC study): a randomized controlled trial. *Hepatol. Int.* **15**, 983–994 (2021).
137. Maiwall, R. et al. A randomized-controlled trial comparing 20% albumin to plasmalyte in patients with cirrhosis and sepsis-induced hypotension [ALPS trial]. *J. Hepatol.* **77**, 670–682 (2022).
138. Krowka, M. J. et al. International Liver Transplant Society practice guidelines: diagnosis and management of hepatopulmonary syndrome and portopulmonary hypertension. *Transplantation* **100**, 1440–1452 (2016).
139. Angeli, P. et al. Albumin infusion in hepatorenal syndrome-acute kidney injury: new evidence challenges recent consensus. *J. Hepatol.* **83**, 800–802 (2025).
140. Mookerjee, R. P. et al. Treatment with non-selective beta blockers is associated with reduced severity of systemic inflammation and improved survival of patients with acute-on-chronic liver failure. *J. Hepatol.* **64**, 574–582 (2016).
141. Singh, V. et al. Asia-Pacific Association for Study of Liver guidelines on management of ascites in liver disease. *Hepatol. Int.* **17**, 792–826 (2023).
142. Elfeki, M. A., Singal, A. K. & Kamath, P. S. Pharmacotherapies for portal hypertension: current status and expanding indications. *Curr. Hepatol. Rep.* **22**, 44–50 (2023).
143. Vashishtha, C., Bhardwaj, A., Jindal, A., Kumar, M. & Sarin, S. K. Effect of midodrine on HVPG in advanced chronic liver disease and acute-on-chronic liver failure — a pilot study. *Liver Int.* **44**, 2714–2723 (2024).
144. Ranjan, A. et al. Midodrine plus propranolol versus propranolol alone in preventing first bleed in patients with cirrhosis and severe ascites: a randomized controlled trial. *Hepatol. Int.* **18**, 1261–1270 (2024).
145. Kulkarni, A. V. et al. Addition of midodrine to albumin reduces the incidence of complications of large-volume paracentesis: an RCT comparing midodrine, terlipressin, and albumin. *Hepatol. Int.* **19**, 1231–1241 (2025).
146. Lesmana et al. Management of acute variceal bleeding: updated APASL guidelines. *Hepatol. Int.* **19**, 1003–1031 (2025).
147. Trebicka, J. et al. Rebleeding and mortality risk are increased by ACLF but reduced by pre-emptive TIPS. *J. Hepatol.* **73**, 1082–1091 (2020).
148. Sujith Reddy, J. S. N. et al. Midodrine versus albumin to prevent paracentesis induced circulatory dysfunction in acute on chronic liver failure patients in the outpatient clinic-a randomized controlled trial. *J. Clin. Exp. Hepatol.* **13**, 576–585 (2023).
149. Condon, S. & Jophlin, L. L. Past, present, and future therapies for alcohol-associated hepatitis. *Clin. Ther.* **45**, 1171–1176 (2023).
150. Maiwall, R. et al. AARC score determines outcomes in patients with alcohol-associated hepatitis: a multinational study. *Hepatol. Int.* **17**, 662–675 (2023).
151. Singh, V. et al. Granulocyte colony-stimulating factor in severe alcoholic hepatitis: a randomized pilot study. *Am. J. Gastroenterol.* **109**, 1417–1423 (2014).
152. Mishra, A. K., Shasthry, S. M., Vijayaraghavan, R., Kumar, G. & Sarin, S. K. Granulocyte colony-stimulating factor improves prednisolone responsiveness and 90-day survival in steroid-eligible severe alcohol-associated hepatitis: the GPreAH study a randomized trial. *Am. J. Gastroenterol.* **120**, 1087–1097 (2025).
153. Kedarisetty, C. K., Kumar, A. & Sarin, S. K. Insights into the role of granulocyte colony-stimulating factor in severe alcoholic hepatitis. *Semin. Liver Dis.* **41**, 67–78 (2021).
154. Nguyen-Khac, E. et al. Glucocorticoids plus N-acetylcysteine in severe alcoholic hepatitis. *N. Engl. J. Med.* **365**, 1781–1789 (2011).
155. Garg, H. et al. Tenofovir improves the outcome in patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure. *Hepatology* **53**, 774–780 (2011).
156. Mack, C. L. et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American Association for the Study of Liver Diseases. *Hepatology* **72**, 671–722 (2020).
157. Tanaka, A. & Harada, K. Acute presentation of autoimmune hepatitis — from acute hepatitis to ALF and ACLF. *Hepatol. Int.* **18**, 1385–1395 (2024).
158. Anand, L. et al. Flare of autoimmune hepatitis causing acute on chronic liver failure: diagnosis and response to corticosteroid therapy. *Hepatology* **70**, 587–596 (2019).
159. Sharma, S. et al. Identifying the early predictors of non-response to steroids in patients with flare of autoimmune hepatitis causing acute-on-chronic liver failure. *Hepatol. Int.* **17**, 989–999 (2023).
160. European Association for the Study of the Liver EASL clinical practice guidelines: autoimmune hepatitis. *J. Hepatol.* **63**, 971–1004 (2055).
161. Sarvesh, S. R. V. et al. Predictors of reversal of acute on chronic liver failure and need for therapeutic goals to extend timelines beyond 90 days [abstract 1631]. *Hepatology* **80**, S2127 (2024) .
162. Wang, H. et al. Reversibility of acute-on-chronic liver failure syndrome in hepatitis B virus-infected patients with and without prior decompensation. *J. Viral Hepat.* **29**, 890–898 (2022).
163. Gustot, T. et al. Clinical course of acute-on-chronic liver failure syndrome and effects on prognosis. *Hepatology* **62**, 243–252 (2015).
164. Chen, G. H. et al. Liver transplantation in acute-on-chronic liver failure: excellent outcome and difficult posttransplant course. *Front. Surg.* **9**, 914611 (2022).
165. Song, D. S. et al. Dynamic analysis of acute deterioration in chronic liver disease patients using modified quick sequential organ failure assessment. *Clin. Mol. Hepatol.* **30**, 388–405 (2024).
166. Bernal, W. et al. Liver transplantation for critically ill patients with acute on chronic liver failure: a prospective national programme of waitlist prioritisation. *Lancet Reg. Health Eur.* **46**, 101067 (2024).
167. Sacleux, S. C. et al. Liver transplant selection criteria and outcomes in critically ill patients with ACLF. *JHEP Rep.* **6**, 100929 (2024).
168. Mahmud, N., Hernaez, R., Wu, T. & Sundaram, V. Early transplantation in acute on chronic liver failure: who and when. *Curr. Hepatol. Rep.* **19**, 168–173 (2020).
169. Kulkarni, A. V. et al. Healthcare utilization and outcomes of living donor liver transplantation for patients with APASL-defined acute-on-chronic liver failure. *Hepatol. Int.* **17**, 1233–1240 (2023).
170. Michard, B. et al. Pretransplant intensive care unit management and selection of grade 3 acute-on-chronic liver failure transplant candidates. *Liver Transpl.* **28**, 17–26 (2022).
171. Sundaram, V. et al. Factors associated with survival of patients with severe acute-on-chronic liver failure before and after liver transplantation. *Gastroenterology* **156**, 1381–1391.e3 (2019).
172. Engelmann, C. et al. Validation of CLIF-C ACLF score to define a threshold for futility of intensive care support for patients with acute-on-chronic liver failure. *Crit. Care* **22**, 254 (2018).
173. Artzner, T. et al. Liver transplantation for critically ill cirrhotic patients: stratifying utility based on pretransplant factors. *Am. J. Transpl.* **20**, 2437–2448 (2020).
174. Bajaj, J. S. et al. Acute-on-chronic liver failure clinical guidelines. *Am. J. Gastroenterol.* **117**, 225–252 (2022).
175. Artzner, T. et al. Location and allocation: inequity of access to liver transplantation for patients with severe acute-on-chronic liver failure in Europe. *Liver Transpl.* **28**, 1429–1440 (2022).
176. Belli, L. S. et al. Liver transplantation for patients with acute-on-chronic liver failure (ACLF) in Europe: results of the ELITA/EF-CLIF collaborative study (ECLIS). *J. Hepatol.* **75**, 610–622 (2021).
177. Thuluvath, P. J., Thuluvath, A. J., Hanish, S. & Savva, Y. Liver transplantation in patients with multiple organ failures: feasibility and outcomes. *J. Hepatol.* **69**, 1047–1056 (2018).
178. Alukal, J. J., Li, F. & Thuluvath, P. J. Liver transplantation within 7-days of listing improves survival in ACLF-3. *Dig. Dis. Sci.* **68**, 3268–3276 (2023).
179. Singal, A. K. et al. High-risk liver transplant recipients with grade 3 acute on chronic liver failure should receive the good quality graft. *Liver Int.* **42**, 1629–1637 (2022).
180. Xia, L. et al. Transplantation for EASL-CLIF and APASL acute-on-chronic liver failure (ACLF) patients: the *TEA* cohort to evaluate long-term post-Transplant outcomes. *EClinicalMedicine* **49**, 101476 (2022).
181. Artru, F. et al. Long-term outcome following liver transplantation of patients with ACLF grade 3. *J. Hepatol.* **82**, 62–71 (2025).
182. Kim, D. S. et al. Asian Pacific Association for the Study of the Liver clinical practice guidelines on liver transplantation. *Hepatol. Int.* **18**, 299–383 (2024).
183. Toshima, T. et al. Outcomes of living-donor liver transplantation for acute-on-chronic liver failure based on newly proposed criteria in Japan. *Clin. Transpl.* **36**, e14739 (2022).
184. MacDonald, A. J. & Karvellas, C. J. Emerging role of extracorporeal support in acute and acute-on-chronic liver failure: recent developments. *Semin. Respir. Crit. Care Med.* **39**, 625–634 (2018).
185. Agarwal, B. et al. Randomized, controlled clinical trial of the DIALIVE liver dialysis device versus standard of care in patients with acute-on-chronic liver failure. *J. Hepatol.* **79**, 79–92 (2023).

186. Maiwall, R. et al. Therapeutic plasma-exchange improves systemic inflammation and survival in acute-on-chronic liver failure: a propensity-score matched study from AARC. *Liver Int.* **41**, 1083–1096 (2021).
187. Beran, A. et al. Plasma exchange for acute and acute-on-chronic liver failure: a systematic review and meta-analysis. *Liver Transpl.* **30**, 127–141 (2024).
188. Kumar, S. E. et al. Therapeutic plasma exchange in patients with acute-on-chronic liver failure improves survival — an updated meta-analysis. *Liver Int.* **45**, e70018 (2025).
189. Kribben, A. et al. Effects of fractionated plasma separation and adsorption on survival in patients with acute-on-chronic liver failure. *Gastroenterology* **142**, 782–789.e3 (2012).
190. Bañares, R. et al. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. *Hepatology* **57**, 1153–1162 (2013).
191. Gerth, H. U. et al. Molecular adsorbent recirculating system can reduce short-term mortality among patients with acute-on-chronic liver failure-a retrospective analysis. *Crit. Care Med.* **45**, 1616–1624 (2017).
192. Bañares, R. et al. Meta-analysis of individual patient data of albumin dialysis in acute-on-chronic liver failure: focus on treatment intensity. *Ther. Adv. Gastroenterol.* **12**, 1756284819879565 (2019).
193. Kumar, S. E. et al. Low volume plasma exchange and low dose steroid improve survival in patients with alcohol-related acute on chronic liver failure and severe alcoholic hepatitis — preliminary experience. *J. Clin. Exp. Hepatol.* **12**, 372–378 (2022).
194. Sharma, A. et al. Fecal microbiota transplantation in alcohol-associated acute-on-chronic liver failure: an open-label clinical trial. *Hepatol. Int.* **16**, 433–446 (2022).
195. Kulkarni, A. V. et al. Primary norfloxacin prophylaxis for APASL-defined acute-on-chronic liver failure: a placebo-controlled double-blind randomized trial. *Am. J. Gastroenterol.* **117**, 607–616 (2022).
196. Kim, S. E. et al. The role of gut dysbiosis in acute-on-chronic liver failure. *Int. J. Mol. Sci.* **22**, 11680 (2021).
197. Jiménez, C. et al. Effect of rifaximin on infections, acute-on-chronic liver failure and mortality in alcoholic hepatitis: a pilot study (RIFA-AH). *Liver Int.* **42**, 1109–1120 (2022).
198. Philips, C. A. et al. Healthy donor fecal microbiota transplantation in steroid-ineligible severe alcoholic hepatitis: a pilot study. *Clin. Gastroenterol. Hepatol.* **15**, 600–602 (2017).
199. Philips, C. A., Ahamed, R., Rajesh, S., Abduljaleel, J. K. P. & Augustine, P. Long-term outcomes of stool transplant in alcohol-associated hepatitis — analysis of clinical outcomes, relapse, gut microbiota and comparisons with standard care. *J. Clin. Exp. Hepatol.* **12**, 1124–1132 (2022).
200. Ahmad, J. et al. Faecal microbiota transplantation with tenofovir is superior to tenofovir alone in improving clinical outcomes in acute-on-chronic liver failure due to hepatitis B: an open label randomized controlled trial (NCT02689245) [abstract PS-163]. *J. Hepatol.* **70**, e102 (2019).
201. Bhushan, B. & Apte, U. Liver regeneration after acetaminophen hepatotoxicity: mechanisms and therapeutic opportunities. *Am. J. Pathol.* **189**, 719–729 (2019).
202. Ben-Moshe, S. et al. The spatiotemporal program of zonal liver regeneration following acute injury. *Cell Stem Cell* **29**, 973–989.e10 (2022).
203. Michalopoulos, G. K. & Bhushan, B. Liver regeneration: biological and pathological mechanisms and implications. *Nat. Rev. Gastroenterol. Hepatol.* **18**, 40–55 (2021).
204. Starkey Lewis, P. et al. Alternatively activated macrophages promote resolution of necrosis following acute liver injury. *J. Hepatol.* **73**, 349–360 (2020).
205. Yang, Y. et al. Novel IL-4/HB-EGF-dependent crosstalk between eosinophils and macrophages controls liver regeneration after ischaemia and reperfusion injury. *Gut* **73**, 1543–1553 (2024).
206. Nautiyal, N. et al. Establishment of a murine model of acute-on-chronic liver failure with multi-organ dysfunction. *Hepatol. Int.* **15**, 1389–1401 (2021).
207. Dubuquoy, L. et al. Progenitor cell expansion and impaired hepatocyte regeneration in explanted livers from alcoholic hepatitis. *Gut* **64**, 1949–1960 (2015).
208. Rastogi, A. et al. Two-tier regenerative response in liver failure in humans. *Virchows Arch.* **464**, 565–573 (2014).
209. Shubham, S. et al. Cellular and functional loss of liver endothelial cells correlates with poor hepatocyte regeneration in acute-on-chronic liver failure. *Hepatol. Int.* **13**, 777–787 (2019).
210. Xiang, X. et al. Interleukin-22 ameliorates acute-on-chronic liver failure by reprogramming impaired regeneration pathways in mice. *J. Hepatol.* **72**, 736–745 (2020).
211. Bihari, C. et al. Bone marrow stem cells and their niche components are adversely affected in advanced cirrhosis of the liver. *Hepatology* **64**, 1273–1288 (2016).
212. Boettcher, S. & Manz, M. G. Regulation of inflammation- and infection-driven hematopoiesis. *Trends Immunol.* **38**, 345–357 (2017).
213. Di Campli, C. et al. Safety and efficacy profile of G-CSF therapy in patients with acute on chronic liver failure. *Dig. Liver Dis.* **39**, 1071–1076 (2007).
214. Qiu, B., Liang, J. X. & Romero Gómez, M. The efficacy and safety of granulocyte colony-stimulating factor in the treatment of acute-on-chronic liver failure: a systematic review and meta-analysis. *PLoS ONE* **18**, e0294818 (2023).
215. Khanam, A. et al. Altered frequencies of dendritic cells and IFN-γ-secreting T cells with granulocyte colony-stimulating factor (G-CSF) therapy in acute-on- chronic liver failure. *Liver Int.* **34**, 505–513 (2014).
216. Roilides, E., Walsh, T. J., Pizzo, P. A. & Rubin, M. Granulocyte colony-stimulating factor enhances the phagocytic and bactericidal activity of normal and defective human neutrophils. *J. Infect. Dis.* **163**, 579–583 (1991).
217. Anand, L. et al. Early cirrhosis and a preserved bone marrow niche favour regenerative response to growth factors in decompensated cirrhosis. *Liver Int.* **39**, 115–126 (2019).
218. Engelmann, C. et al. Granulocyte-colony stimulating factor (G-CSF) to treat acute-on-chronic liver failure: a multicenter randomized trial (GRAFT study). *J. Hepatol.* **75**, 1346–1354 (2021).
219. Engelmann, C. et al. Combination of G-CSF and a TLR4 inhibitor reduce inflammation and promote regeneration in a mouse model of ACLF. *J. Hepatol.* **77**, 1325–1338 (2022).
220. Cui, Y. L. et al. Recombinant human hepatocyte growth factor for liver failure. *Contemp. Clin. Trials* **29**, 696–704 (2008).
221. Pusic, I. & DiPersio, J. F. Update on clinical experience with AMD3100, an SDF-1/CXCL12-CXCR4 inhibitor, in mobilization of hematopoietic stem and progenitor cells. *Curr. Opin. Hematol.* **17**, 319–326 (2010).
222. Lin, B. L. et al. Allogeneic bone marrow-derived mesenchymal stromal cells for hepatitis B virus-related acute-on-chronic liver failure: a randomized controlled trial. *Hepatology* **66**, 209–219 (2017).
223. Wang, Y. H. et al. The high level of IL-1β in the serum of ACLF patients induces increased IL-8 expression in hUC-MSCs and reduces the efficacy of hUC-MSCs in liver failure. *Stem Cell Res. Ther.* **14**, 231 (2023).
224. Zheng, Y. et al. Serum from acute-on-chronic liver failure patients may affect mesenchymal stem cells transplantation by impairing the immunosuppressive function of cells. *J. Clin. Transl. Hepatol.* **9**, 503–513 (2021).
225. Xu, W. X. et al. Combination treatments of plasma exchange and umbilical cord-derived mesenchymal stem cell transplantation for patients with hepatitis B virus-related acute-on-chronic liver failure: a clinical trial in China. *Stem Cell Int.* **2019**, 4130757 (2019).
226. Li, Y. H. et al. Umbilical cord-derived mesenchymal stem cell transplantation in hepatitis B virus related acute-on-chronic liver failure treated with plasma exchange and entecavir: a 24-month prospective study. *Stem Cell Rev. Rep.* **12**, 645–653 (2016).
227. Lin, D. et al. Mesenchymal stem cells exosomal let-7a-5p improve autophagic flux and alleviate liver injury in acute-on-chronic liver failure by promoting nuclear expression of TFEB. *Cell Death Dis.* **13**, 865 (2022).
228. Zhang, J. et al. Potential networks regulated by MSCs in acute-on-chronic liver failure: exosomal miRNAs and intracellular target genes. *Front. Genet.* **12**, 650536 (2021).

Author contributions

S.K.S. and A.C. researched data for the article, contributed substantially to discussion of the content and reviewed and/or edited the manuscript before submission. All authors wrote the article.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41575-025-01159-4.

Peer review information *Nature Reviews Gastroenterology & Hepatology* thanks Robert Schierwagen; Carmine Gambino, who co-reviewed with Roberta Gagliardi; and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

© Springer Nature Limited 2026

[1]Department of Hepatology and Liver Transplant, Institute of Liver and Biliary Sciences, New Delhi, India. [2]Department of Molecular and Cellular Medicine, Institute of Liver and Biliary Sciences, New Delhi, India. [3]Division of Gastroenterology, Hospital of the University of Pennsylvania, Philadelphia, PA, USA. [4]Division of Gastroenterology and Hepatology, Department of Medicine, National University Health System, Singapore, Singapore. [5]Department of Infectious Diseases, Tongji Hospital, Tongji Medical College and State Key Laboratory for Diagnosis and Treatment of Severe Zoonotic Infectious Diseases,

Huazhong University of Science and Technology, Wuhan, Hubei, China. [6]Department of Hepatology, Selayang Hospital, Batu Caves, Malaysia. [7]Division of Gastroenterology and Hepatology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. [8]Department of Gastroenterology and Hepatology, Saitama Medical University, Saitama, Japan. [9]State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Centre for Infectious Diseases, Collaborative National Clinical Research Centre for Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China. [10]Division of Gastroenterology (Liver Unit), Department of Critical Care Medicine, University of Alberta, Edmonton, Alberta, Canada.